Archives of Dermatology and Syphilology

VOLUME 4 OCTOBER, 1921 NUMBER 4

PSEUDOXANTHOMA ELASTICUM *

BINFORD THRONE, A.B., M.D.

BROOKLYN

AND

HERMAN GOODMAN, B.S., M.D.

WITH HISTOLOGIC REPORT BY D. S. D. JESSUP, M.A., M.D.

NEW YORK

HISTORICAL SKETCH

In 1884, F. Balzer [1] made a clinical and histologic study of a case which presented unusual and unique characters not theretofore described. The most conspicuous feature of the disease was its clinical resemblance to xanthoma, or xanthelasma, and its histologic changes which did not suggest the pathology of that condition. Fortunately, a complete and careful study of the patient was made both before and after death, so that there can be no question as to the identity of the disease.

In 1889, Chauffard reported a case as xanthelasma disseminatum et symmetricum. The patient was later examined and observations were published by Besnier and Doyen. Hallopeau and Lafitte also had the opportunity of studying the same patient.

In 1896, it fell to Darier's [2] lot to study the same patient. For the first time, histologic examinations were made, and the similarity to Balzer's case was recognized. Darier coined the name of pseudoxanthoma elasticum, because the disease, although rare, had some clinical and histologic features which were so well defined that the disease deserved a name to distinguish it as a clinical entity. Histologically, the characters of fragmentation, with swelling, and finally complete degeneration of the elastic network merited the name "elastorrhexis," which appellation Darier has also given the disease.

---

* From the New York Skin and Cancer Hospital.

1. Balzer: Recherches sur les caracters anatomique du xanthelasma, Arch. de physiol. norm. et path. Ser. 3, **4**:64, 1884.

2. Darier: Pseudoxanthoma elastique, 3rd International Congress of Dermatology, London, 1896, p. 289.

Up to the present time, fifteen cases have been reported and six others mentioned in the literature.

Elastoma and nevus elasticus must be added to the names already given as having been applied, but pseudoxanthoma elasticum is most generally used.

COMPOSITE CLINICAL PICTURE

Pseudoxanthoma elasticum has presented great similarity of clinical features wherever it has been studied. It appears in youthful persons and in adults of both sexes, and more than one member of the family may be affected. The skin changes are usually symmetrical. The localizations of preference are the covered parts of the body, especially the regions of the great articular folds—the axillae, groins and bends of the elbows—and the uncovered portions, such as the neck, less often the hands and rarely the face.

The eruption consists of round or oval, hemispherical, smooth, shiny, pinhead (hempseed, millet seed, lentil seed) to pea sized papules. Their color may be mild yellowish mixed with violet, or less often brownish, ivory or colorless. The papules may be isolated, grouped, or confluent into plaques or linear formation. The clinical picture often gives the impression of a fine network, or meshlike pattern or trellis work. The affected areas may be surrounded by perifollicular spots of the same appearance formed of slightly prominent soft yellowish papules. The skin may be soft or slightly infiltrated, it may be wrinkled, and that of the articular folds may be greatly relaxed or even pendulous.

The affection remains limited for years or may increase in area. Change or evolution in the lesions or stage formation has not been previously mentioned. The subjective symptoms are nearly always absent, although mild itching has been noted.

Although several writers have referred to the lesions as xanthoma-like or xanthelasmatic, the clinical analogy to xanthoma is slight. The regions ordinarily the site of xanthoma are usually free in pseudoxanthoma elasticum, although localization on the face has been given. In one case it is admitted that the identity of the lesions on the face and those of pseudoxanthoma elasticum on the same patient could not be established.

COMPOSITE HISTOLOGIC PICTURE

The microscopic appearance, as given by various authors, may be described as follows: There is a change in the elastic fibers of the middle and deep portions of the corium generally considered a degeneration, and variously mentioned as a swelling, proliferation, splitting up and breaking up into fragments. Darier has termed this "elastorrhexis." Islands of these altered fibers, of different sizes, are found scattered

through the corium and surrounded by normal collagen. The transition between normal and degenerated elastic fibers has been noted. The changes in the upper derma and epidermis are insignificant, and the sweat and sebaceous glands, hair follicles and blood vessels are normal. The so-called xanthoma cell of true xanthoma has not been found, and Bodin [3] alone has found the giant cells, called Bodin cells, about the lesions in the region of the blood vessels. Bodin lays considerable stress on the cells, describing them in detail, including the fact that some of them contained fragments of elastic fibers. Their presence in his case suggests the rôle of the foreign body giant cell so often seen in the processes of degeneration and inflammation.

CLINICAL CASE REPORT

History.—Mrs. A. E., an American woman of German parentage, 39 years old, was born in New York City and had never left the country. Her father had died at the age of 53 years, probably of kidney complications, the result of chronic alcoholism. Her mother was well. Neither parent had ever shown a skin condition similar to that of the patient. She had three brothers and one sister. None of the brothers, who were all well, have ever shown any evidence of a similar skin disease. The sister, who died at the age of 34 of pulmonary tuberculosis, showed the same condition as the patient. It appeared when she was 4 years old. The skin of the entire circumference of the neck was involved; but the folds, which our patient has had for the last four or five years, were never present in the case of the deceased sister. No other portion of the skin of the sister was ever affected by the disease.

The patient and her sister were the only ones of the known circle of relatives who had shown this particular type of skin disturbance. The patient had a child who was free from any like condition.

Mrs. A. E. had the usual diseases of infancy, and specifically mentions the acute exanthems, measles and scarlet fever, and also diphtheria. At the age of 18 months, an abscess of lymph node in the left axilla was incised. The scar from this procedure is still present.

General Examination.—The patient was a small, slight woman. Her height was 5 feet, 1 inch, and her weight about 99 pounds. She appeared only fairly well nourished. Physical examination revealed that the heart and lungs were apparently sound, and neither in the liver nor other abdominal organs could any abnormalities be detected. Enlarged lymph nodes could not be palpated in the neck, in the axillae or in the inguinal regions.

Roentgen-ray examination of the chest revealed nothing abnormal in the lungs, but did show enlarged mediastinal lymph nodes.

The first urine examination of a casual specimen was reported acid in reaction, clear, and with a specific gravity of 1.021. There were no casts, and the examination for albumin was negative. There was a slight trace of indican. The diacetic acid test was negative, but there was a heavy trace of acetone and a faint trace of sugar.

3. Bodin: Pseudoxanthoma elastique, Ann. de dermat. et syph. Ser. 4, **1**:1073, 1900 (with histologic cut and illustration of Bodin cells).

Another specimen of urine was examined after the patient had been asked to abstain from eating candy, in which she had frequently indulged, having been employed in a candy factory. This and later specimens were negative for sugar. The Wassermann reaction was negative.

The blood chemistry was:

Alkaline reserve	43	(Normal 50-55)
Creatinin mg. per 100 c.c.	2.3	(Normal 1-2)
Sugar mg. per 100 c.c.	166	(Normal 75-120)
Urea	13	(Normal 11-15)
Uric acid	1.1	(Normal 1-2)

From this it can be seen that the laboratory tests were negative. The slight increase in the blood sugar and the slight trace of sugar found in the first specimen of urine were due to an excessive intake of sugar.

Skin Condition.—The lesions of the skin under discussion first appeared on the neck of the patient when she was 4 years old. The other areas, which now show the affection, appeared in an unnoted order. The patient was certain that the various types of eruption which she had, and which will later be described, had always appeared as they did when she presented herself, except that the wrinkling which was so evident on the neck and on the axillary surfaces of the arms, was supposed to have been present only for the last four or five years. The lesions had never been troublesome, and the patient came for treatment only for cosmetic purposes.

The lesions involved the skin of the entire circumference of the neck, the inner third of both clavicular regions, the suprasternal notch, the axillae and the cubital flexures extending from the middle of the arm to the middle of the forearm. No lesions could be found on the face, the hairy scalp, the lower abdomen, the inguinal regions or the popliteal spaces.

Types of Lesion.—For clarity of description, and in order to convey a comprehensive conception of the case, three types of lesion must first be described in detail. Whether or not there is any relation between these three, whether they are stages or phases one of the other, or whether they are independent characters of the disease, remains a matter for speculation.

The first type of lesion is from 1/64 to 1/16 inch in diameter. It is a circumscribed, elevated, smooth, papular, infiltration of fresh butter yellowish hue. These lesions are irregular in outline, with straight rather than curved periphery. Some of the lesions are round or irregularly oval. The sides of the papule may be straight instead of sloping. These lesions may be isolated, especially at the borders of the other lesions at the neck. They may be grouped in twos and threes, or two or three may be confluent, that is, have one border in common, but the individual character of each is not completely lost in the combination. Some lesions of the neck of this type appear to be arranged in irregular lines that run in all directions, transversely, longitudinally and diagonally, and the lines appear to run together frequently, forming a sort of network effect. The skin between these lesions is slightly grayish pink in color, and the capillaries appear slightly dilated and telangiectatic. This skin appears thinned also.

The second type of lesion is a raised plaque, perhaps 1/16 or 1/8 inch above the surface of the normal skin. The plaques are of various areas from half an inch to a side to 2 or 3 inches. The borders of the plaques are sloping, regular and sharp in some places with a fading off in others, at times into areas of normal skin and at other times into small areas of the individual lesions such as described in the foregoing, that is, the small lesions appear at the borders of the

Fig. 1.—Pseudoxanthoma elasticum (slightly enlarged) showing the individual lesions and part of one raised plaque from side of neck. This illustration was made by Alfred Feinberg.

UNIV OF MICH.

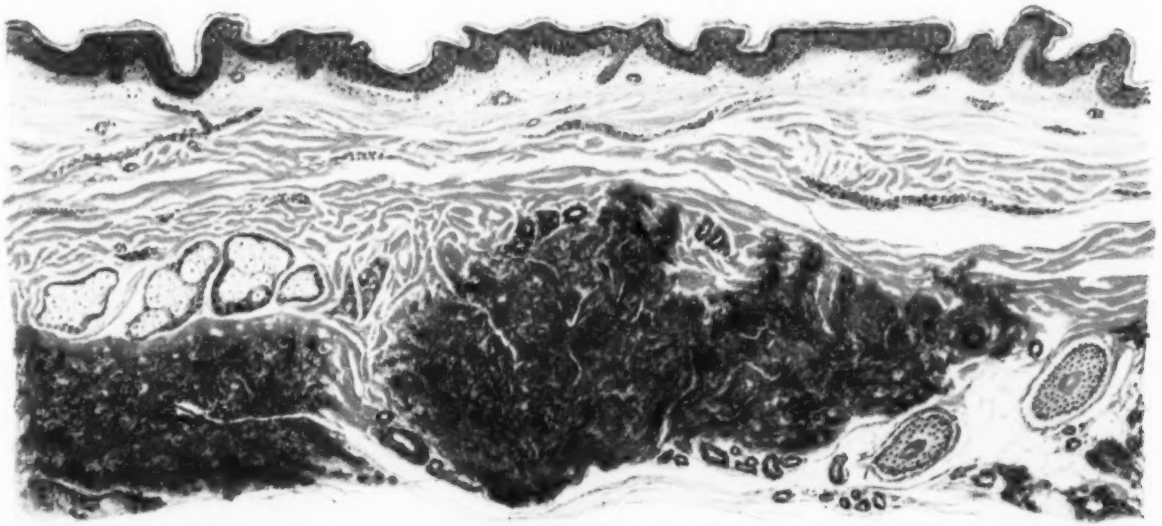

Fig. 2.—Pseudoxanthoma elasticum (New York Skin and Cancer Hospital Path. No. 5,444). Low power colored drawing (by Eva Carrington). Hematoxylin stain. The degenerated elastic tissue stained purple, together with the intermingled collagen fibers showing basic staining, form the deeply stained masses in the lower derma. In normal skin the elastic fibers would be invisible with this stain and the deep derma would only show the collagen fibers stained red with eosin as seen in this drawing in the upper derma.

UNIV. OF CH.

Fig. 3.—Pseudoxanthoma elasticum (New York Skin and Cancer Hospital Path. No. 5,444). Low power colored drawing (by Alfred Feinberg). Weigert's hematoxylin nerve tissue stain. This stain has a selective action for the degenerated elastic fibers in the middle and deep derma which stand out as distinct black masses. The normal elastic tissue is not shown by this stain.

UNIV. OF MICH.

larger plaques. The surface of the plaque is not smooth, but roughened and moderately granular. One may conceive rather than perceive, the preexisting small lesions in the plaque.

The third type of lesion is limited to the flexor surface of the arms. The lesion is a flattened plaque, not perceptibly raised above the normal skin, and of a lighter tawny yellow. This lesion could be readily overlooked during a casual and superficial examination of the patient. The surface is smooth, except for the depressions of the mouths of follicles which are more prominent in this type of plaque than in the raised plaque.

To the touch, the lesions of the first type are exceedingly soft individually, but the skin surface from which they rise is harder than normal, more leathery than ordinary skin and gives a greater resistance when picked up between the fingers. The raised plaques are doughy and nonelastic. The flat plaques of the flexures of the arms are not infiltrated.

In the neck, the creases are extremely exaggerated and more or less permanent. The slightest movement of the neck increases the depth and intensity of the creases. When the patient has her head at rest in the normal position, the creases are still to be seen, but not so readily as when the head is rotated laterally. No matter how much effort is made to tilt the chin upward, the skin of the anterior portion of the neck is never at a stretch—there is always a redundancy. In the axillae, this feature of the disease is very noticeable, and with the arms at right angles to the body the skin of the axillae hangs pendulous and in folds.

No areas of the skin surface other than those given as the site of the disease process shows any abnormality of texture, nor is there any exaggeration of the wrinkles such as any woman of 39 is likely to have. The patient had several pigmented moles.

The distribution of the three types of lesions is interesting. On the anterior surface of the neck, and encroaching a little toward the left, there is a preponderance of the isolated individual lesions of Type 1. On the sides of the neck, and covering the posterior aspect entirely are the raised plaques of Type 2. These two types are present together in the axillae, the apex of the axilla having more of the plaques, while the limits of the axilla have the individual lesions. As mentioned before, the plaques of Type 3 are present alone on the flexures of the arms and forearms.

It is worthy of note that the scar in the left axilla shows no lesions of the three types described.

Histologic Changes.—(Report of Dr. D. S. D. Jessup of the New York Skin and Cancer Hospital, Path. No. 5444). Tissue was excised from a lesion of the arm near the axilla. Paraffin sections were made and stained by hematoxylin-eosin, Verhoeff's, and Weigert's elastic tissue stains, Mallory's anilin blue stain, Van Gieson's picric acid fuchsin, Unna's polychrome methylene blue stains and Weigert's hematoxylin nerve tissue stain.

The epidermis is thin with a loss of the pegs, and it is thrown up into folds by prolongations of the derma. There are a few scattered pigmented cells in the epidermis and upper papillary portions of the derma and a few mast cells. There is no cellular exudate and in other respects these regions are normal. The noteworthy changes are in the middle and deeper portions of the derma and are most strikingly brought out by the hematoxylin-eosin stain. Here, instead of the normal bundles of collagen fibers stained red with the eosin, there are irregular islands or masses of deep purple staining tissue. They take the stain seen in calcareous deposits. Examined under the high power, there is

a tangled network of short fibers, fine or coarse, and appearing as granules or short rods when in transverse or oblique section. The lesion is in bands parallel to the surface of the skin and in some places is broad enough to occupy the whole middle and lower derma down to the subcutaneous fat. The surrounding collagen fibers stain normally, but those interspersed in the purple staining areas show varying degrees of the basic stain such as is seen in basic degeneration. This is brought out by the Verhoeff and Weigert elastic tissue stains in which there is sharp contrast between the deeply stained elastin and less deeply stained elacin and the clear red of the collagen, which with these two stains—does not show basic degeneration. The affinity of the elastic fibers for the basic stain in the hematoxylin-eosin sections is characteristic of degenerating elastic tissue so that they are not seen in the normal derma with this stain.

With Unna's polychrome methylene blue the degenerating elastic fibers appear as glistening unstained granules with pale blue stain of the collagen in the lesion. In the Van Gieson sections the elacin fibers appear as yellow granular clumps. The collagen stains a paler pink than normal and does not give the yellow reactions seen in colloid milium with this stain. Mallory's anilin blue shows a varying intensity of the blue of the collagen fibers in the lesions as though

Fig. 4.—Pseudoxanthoma elasticum, showing the character of the skin of the neck and the left axilla. The increased nature of the folds, and the almost pendulous reduplication should be noted.

there were some degeneration and loss of staining power. The elastic fibers are in granular masses stained pink or orange. With a view to determining whether the nerve fibers were altered, Weigert's hematoxylin nerve tissue stain was employed. No changes were noted in the nerve fibers, but the stain brought out most strikingly the degenerated elastic fibers in the deep derma. The stain has a selective action for elacin, staining the swollen fibers and granules a deep black, but the normal elastin is unstained, and the rest of the tissue in the section, stained pale brown, is in marked contrast to the black elacin.

There are no changes from normal in the blood vessels, sweat and sebaceous glands, and in the tissue sectioned the hair follicles do not show any of the changes that might be expected from the clinical appearance of some of the lesions. There are no cells of the type seen in true xanthoma and no giant cells. The various stains lead to the conclusion that the lesion is a degeneration of the elastic tissue in the deeper portion of the derma and a moderate change

also in the collagen in the lesions. The elastic fibers compared with those of normal skin are swollen and irregular in outline and have lost their normal reaction to the various stains showing the changes of elacin or degenerated elastin. At the edge, the normal elastic fibers appear to be continuous with the degenerated ones.

COMMENT

In our opinion, based on the clinical aspects alone, the primary lesion of pseudoxanthoma elasticum is the individual papule, designated as Type 1. By confluence, the raised plaque of Type 2 is formed. The

Fig. 5.—Case of pseudoxanthoma elasticum observed in the service of Dr. A. S. Clark, New York Skin and Cancer Hospital.

larger plaques of the raised type, as seen on the back of the neck, seem to be due to the confluence of smaller plaques, and this appeals to us as accounting for the granular appearance of the larger plaques. The presence of individual lesions at the borders of the plaques seems to show a progressive development where these are found, namely, on the neck and in the axillae. On the other hand, the plaque of so-called Type 3 seems to have been formed from lesions developing at one

time. The absence of individual lesions at the border of the last type of plaque seems to sustain this view.

Unfortunately, the patient did not permit a sufficient number of biopsy examinations to add any histologic evidence to this theory. We must say that during the period that the patient was under our observation, from April, 1920, to the date of the present writing, there has been no visible change in the clinical manifestation.

REVIEW OF THE LITERATURE

The following review of the literature consists of rather full abstracts of case reports, with clinical and histologic data. Important generalizations, discussions, etc. are not included under this heading, but will be found in another section of this paper.

Balzer's[1] *Case.*—Balzer reported the case of a man, aged 49, a mason, admitted to the Hospital Saint Louis on Oct. 26, 1882, with pulmonary tuberculosis. According to his statements, his mother had died as a result of chronic lung disease. The patient had had intermittent fever during his military service. Since that time he had been in good health until he commenced to cough in April, 1881. He stated positively that he had never had jaundice.

During the past year he had had several small hemorrhages and had become progressively weaker, so that he had been unable to work for seven months. He had slightly improved by treatment. For several months he had suffered from headache coming on in the morning but ceasing during the day. Quinin sulphate and sodium salicylate relieved these headaches to a great extent. During the month of November, he had had severe chills several times a week, with a rise of temperature to 39.5 C. Physical examination showed a cavity at the right apex with souffles; at the left apex there were subcrepitant râles and disseminated moist râles over the entire chest, predominating on the right. There were no pathologic heart signs. Loss of appetite and persistent diarrhea were symptoms.

Numerous xanthelasmatic plaques covered the surface of the body, which the patient stated he had noticed since childhood. The condition had been more noticeable when he was young. The plaques were like those of xanthelasma planum, pale yellow in color, visible especially on pressure. They were irregularly distributed, and very variable in size, varying from 1 sq. mm. to 1 sq. cm. They were especially numerous around the navel, where they were slightly raised. The plaques were less numerous on the chest and on the back. They were also numerous on the neck, especially at the back; they followed the folds of the skin, and their longest axis lay parallel with these folds. The patient's face was yellow, but there were no real signs of jaundice in the conjunctivae or in the urine. On the limbs the yellow plaques were especially numerous in the folds of the elbow and axillae, less so in the groin and at the knees.

The diarrhea resisted all treatment, and the patient grew rapidly weak and cachetic. He died on November 29.

Necropsy examination showed the lungs covered with tubercles and fibrocaseous masses; there were numerous adhesions, and cavities in both apexes. The liver was large and of the color of yellow ochre. Subsequent microscopic examination showed simply a fatty liver without any special lesion. The

kidneys were slightly sclerotic. The spleen was normal. The most interesting changes were seen in the heart. The right auricle showed a light yellow color on its inner surface without any evident thickening of the endocardium. This yellow coloring was visible throughout the columnae carneae, but not on their posterior aspect and not in the auricle. This coloration resembled somewhat that of the plaques in sclerosis of the endocardium, but the appearance of the membrane was duller and more opaque than in sclerosis. It could also be seen, though less clearly, on the pericardium.

Careful histologic examination of the xanthelasmatic plaques of the skin and the heart were made. After hardening in absolute alcohol sections were prepared in various ways: (1) staining with picrocarmine and mounted in glycerin; (2) staining with eosin dissolved in alcohol, and mounted in a potash solution of from 10 to 40 per cent.; (3) other sections first placed in potash solution were later stained with methylene blue or picrocarmin and then mounted in glycerin. When fat was present in sufficient quantities to interfere with the examination, sections were treated with ether, essence of clove and absolute alcohol before being stained.

The sections treated with eosin and 40 per cent. potash solution gave the best results. It is advisable, however, to use several methods and to make several series of examinations.

With the low-power of the microscope, several plaques were seen in a single section, usually lying immediately beneath the pars papillaris and separated from the epidermis by a layer of normal tissue of variable thickness. The plaques varied greatly in size and shape, some being long and some round. They were formed of fibrous tissue which the picrocarmin colored rose and of a material that picric acid colored greenish yellow. Under the high power it was seen that this material was the elastic tissue which was remarkably altered. The connective tissue was thickened and formed a fascicle enclosing the irregularly shaped plaques, thus outlining the space filled by this altered elastic tissue. The elastic tissue was increased. Its fibers appeared more numerous than normal because they were hypertrophied, split and segmented transversely. Sometimes their fragments were entirely broken off so that they looked like irregular crystals; sometimes they remained end to end resembling mycelium hyphae. The change commenced by a tumefaction of the fibers, which then split and finally separated transversely. The fragments usually remained close together following the direction of the original fibers. Sometimes these fragments were in a continuous line with normal elastic fibers. The size and shape of these fragments were variable, ranging from segments similar to crystals to small elastic grains. More rarely the splitting took place lengthwise; in this case their histochemical composition appeared to be altered, as they did not stain well with picric acid; and eosin and potassium gave them a violet red shade deeper than normal fibers. Sometimes, on the contrary, they resisted all stains and remained dull and pale. There was little fat and few xanthelasmatic cells. In some sections the elastic fibers were entirely destroyed, leaving compact masses of irregular opaque granulations. The process was everywhere the same—in the small disseminated plaques and the larger plaques whether superficial or deep in the skin, and in the plaques of the heart walls.

Darier's[2] *Case.*—Darier reported the case of a man, aged 42 years, under the title of pseudoxanthome elastique. The family history was not important. The patient had had typhoid at the age of 23; then alcoholic gastritis with repeated hematemesis and jaundice; also malaria. There were signs of indura-

tion, probably tuberculous, at the apexes of both lungs. The blood was normal. The urine did not contain sugar.

When 26 years old, he had noticed a livid spot in the folds of the elbow joint, which itched slightly. This soon became yellow and had remained so since that time. Other regions were attacked soon after, and the condition had progressed steadily. At the time of the report it extended symmetrically along the skin folds of the trunk and of the large joints of the limbs—that is to say, the neck and clavicular region, the elbows, the abdomen below the navel, the under surface of the penis, the inguinofemoral region, between the buttocks and the posterior surface of the knees. The lesions consisted of large spots or plaques resembling xanthoma, of a yellowish café au lait color. The plaque on the elbow measured 5 by 10 cm. On close examination it was evident that the plaques were formed by the confluence of small miliary spots of a creamy white color, arising from a reticular base of violet or lilac shade. The skin in the vicinity was tender to the touch, slightly doughy in consistency, relaxed and less elastic than normal. Around the plaques were small yellow papules, surrounded by an areola, with a pigmented follicular orifice in the center, similar to "diabetic xanthoma." The back, the breast, the extensor surface of the limbs, the hands and the feet showed no lesions. The head was not much affected, but there was a small yellowish spot on the palpebral commissure of both eyes, and spots of a dull white, confluent at certain points with a vascular base, on the mucosa of both lips and on the inner surface of the cheeks.

Histologic examination was made of specimens taken from different sites, prepared with different reagents, and different stains were used on the sections. The technic giving the best results was orceinic acid for study of the section as a whole, and eosin and potash in 40 per cent. solution, or osmic acid and safranin, with decoloration by tannin, for the study of details.

With low power microscope, it was evident that the lesions were made up of elastic tissue at the level of the corium. This tissue was augmented more by the enlargement and twisting of the fibers than by a true hypertrophy. In the plaques of the axilla, for example, this alteration of the elastic tissue extended from beneath the pars papillaris to the hypoderm in the form of a continuous layer in which, however, imperfect lobulation could be observed, and a tendency to form round lumps, more or less confluent or separated by healthy fibers. Sections of isolated papules showed alteration of the elastic tissue around a pilosebaceous follicle, which it surrounded like a crown.

With a high power microscope, it could be seen that the elastic tissue fibers were thickened and enlarged and often broken into fragments. These fragments, in the shape of rods or short cylinders, remained in contact, thus resembling chains of large bacilli. More frequently the fibers were swollen and beaded, oddly twisted, with vacuoles and longitudinal fissures. In some cases they had become veritable plaques with a number of vacuoles. In other cases they had completely disintegrated into amorphous masses of clots or granulations. These changes merited the names of elastoclasia or elastorrhexia, by which the author designates them. In a number of ways it was easy to show that these peculiar formations were in direct continuity with the normal elastic fibers, when at a certain point, the normal formation abruptly took on the character of elastorrhexia.

At the same time, these morphologic changes produced some chemical changes in the elastic tissue. The granulations were less resistant to potash, stained less readily with acid stains, but slightly with basic dyes. They stained violet with hematin.

The connective tissue, as shown in different preparations, was not noticeably sclerotic in the neighborhood of the elastorrhexia; the cells were slightly increased in number next to the altered elastic fibers; some connective tissue cells showed granulated protoplasm, but these did not stain with osmic acid and did not resemble in any way xanthoma cells. It is important to point out that xanthoma cells were not found in any of the sections examined.

Bodin's[3] *Case.*—Bodin made a study of a man aged 50 who had entered the hospital of Rennes for bronchitis of several months' duration; there was nothing of interest in his family or personal history. He had been in good health until he began to cough. When he entered the hospital he was thin and weak and had night sweats. Examination of the chest showed signs of tuberculosis in both lungs, especially at the apexes. The character of the sputum confirmed the diagnosis. Digestive troubles were also noted, including loss of appetite and diarrhea, but examination of the liver showed nothing of note, and he had never had jaundice. The urine was normal and did not show sugar. For thirty years the patient had had numerous skin lesions to which he had given no special attention, as they had never given him any trouble and had increased only slightly since they first appeared. The lesions were particularly numerous on the abdomen below the umbilicus, extending symmetrically on each side of the median line, and reaching a size larger than the palm of the hand. The lesions elsewhere were also absolutely symmetrical—in the clavicular region, the axillary region, the inner surface of the arm and the anterosuperior surface of the forearm, and the interior upper surface of the thigh. The lesions were arranged in plaques of more or less regular shape, in the center of which the elements of the dermatosis were seemingly confluent but actually separated by small spaces of normal skin. Toward the edge of the plaque they were separated from each other and gradually diminished in size until at the outer edge they were small punctiform spots. Closer study of the lesions showed that these elements were all similar, pale yellow, sharply defined, varying in size, being oval or rounded, apparently homogenous or slightly granulated. At the surface of the skin, they formed a slight projection which could be easily seen and felt, but the skin around them appeared to be absolutely normal. Palpation revealed no induration and caused no pain.

For histologic examination two pieces were excised from the abdominal lesions, fixed with sublimated acid (formula of Nicolle), then mounted, some sections in paraffin and some in gum, and treated with various stains. Under a low power microscope the lesions were seen to be situated superficially in the derma at the level of the upper part of the reticular layer, above the sweat glands, with which they had no relation. Their upper surface did not reach the papillary layer. In section they were ellipsoid in shape, the long axis being parallel to the cutaneous surface, measuring from 300 to 400 microns on their long diameter, and from 0.4 to 0.6 mm. on their short diameter. At the surface, there were small irregular masses of granulated matter situated between the connective fibers of the derma, which were crowded together around them. Below these lesions the derma was normal; above them the pars papillaris was also normal. The walls of the small vessels were slightly thickened and showed a slight round-cell infiltration. In some places the pars papillaris appeared slightly thinner over these lesions, but the difference was only slight. In the epidermis, this thinning, corresponding to the xanthomatous elements, was more marked, especially in the mucous layer. Subcutaneously the fat globules were abnormal; the fat cells composing them were separated from

each other, and when stained with osmic acid, the fat was seen to have accumulated at one pole. The rest of the cell appeared to be filled by a liquid.

When the xanthomatous lesions were examined under the high power three different elements were found: (1) small masses of granulations, (2) connective tissue, (3) special cell elements, mostly around the vessel walls.

1. The small granulations were made up of tissue which showed the histochemical characteristics of elastic tissue; they stained yellow with picrocarmin; eosin stained them rose; methylene blue and orcein stained them equally well. If, after staining with eosin, the sections were mounted in 40 per cent. potash solution, they kept the rose color of the elastic fibers in the rest of the tissue completely decolorized. They showed, however, a more violet tinge than normal elastic tissue treated with the same stain. The small masses of elastic tissues appeared broken up into irregular crystal-like fragments. The continuity of these fragments with normal elastic fibers was less frequently seen than in Balzer's case, but otherwise their appearance corresponded exactly to the descriptions of Balzer and Darier.

2. Between the masses of elastic tissue fragments, the connective tissue was broken up and crowded around these masses, but it did not appear to be altered in its histologic characteristics, except that there was an increase in the number and size of the connective tissue cells.

3. No xanthomatous cells, such as are typical of true xanthoma, were found, but there were a number of giant, polymorphonuclear cells of variable size and shape. These were found in the vicinity of the vessels, chiefly at the edge of the lesions. There was considerable variation in the morphology of these cells. Many were giant cells of variable size, some as large as 50 by 30 to 45 microns with uniform granular protoplasm and a number of round or oval nuclei. Other giant cells were represented by their nuclei alone or showed little protoplasm. Others showed signs of beginning degeneration—there were some giant cells of irregular outline with nuclei that did not stain normally, some with hyaline degeneration of the protoplasm and others with a degenerating protoplasm which showed staining reactions similar to those of the elastic tissue fragments. On close examination some of the giant cells seemed to be almost completely assimilated by the elastic tissue, with scarcely any nuclei and only a few fragments of the original cell showing marked degeneration; or an elastic tissue fragment might be enclosed completely or partially in a degenerating giant cell.

Von Tannenheim's[4] *Case.*—Von Tannenheim's case was posthumously reported. He had observed the case of a woman aged 76. She was moribund when she came to the hospital, and no history was obtainable. The lesion was first found at necropsy. The skin in general was pale and slightly pigmented. On the anterior side of both upper arms and thighs and on both sides of the iliac crest were yellowish or opaque infiltrating lesions, irregular in shape, the size of millet seeds, but confluent and forming plaques where most numerous. On section they appeared as dry yellowish white foci in the the cutis, the epidermis appearing unaltered. A few lesions were noted under the skin and on the sides of the thorax.

Necropsy examination revealed in addition: arteriosclerosis, endocarditis, myocarditis, lobular pneumonia, intestinal hemorrhage and senile marasmus.

---

4. Von Tannenheim: Zur Kenntniss der Pseudoxanthoma elasticum (Darier), Wien. klin. Wchnschr. **14**:1033, 1901 (with two histologic cuts).

Pieces of skin were taken from the upper arm and the thigh for histologic examination, and preserved in alcohol, liquor formaldehydi, Zenker's and Muller's solutions. Sections were mounted in celloidin.

With the lower power unstained sections showed opaque, oval lesions not clearly defined in the upper layers of the corium, the pars papillaris being attenuated and flat. The lesions were separated from the epidermis by apparently normal connective tissue. The oval lesions showed the diameter parallel to the skin surface. They did not extend into the subcutaneous tissue nor to the sweat glands. They appeared to be composed of granulated opaque sections which in places were separated from each other by homogeneous, sometimes swollen connective tissue fibers. When more closely observed this granulated tissue was seen to be in direct continuity with strong, glossy fibers in the surrounding tissue. These fibers, as they entered the lesion, were split up and twisted into knots until they disappeared in the opaque lobules. In some sections these lesions appeared darker and the outlines of the knotted fibers clearer and sharper. The addition of dilute sulphuric acid produced gas bubbles and calcium sulphate crystals, indicating calcification and the deposition of carbonate of lime.

On staining with hematoxylin-eosin, the opaque portions of the lesion were seen to be composed of red staining fibers or coils, or spirally twisted bands, which under the high power appeared as grandular, curved sometimes glistening masses. Between these masses the connective tissue was sometimes normal in appearance, but sometimes the fibers were homogeneous, swollen and also stained red.

The pars papillaris of the corium, as noted in the foregoing, was much thinned; otherwise the skin showed little change.

Every staining method to demonstrate elastic tissue showed that these lesions give the same reaction. The opaque coil-like parts of the lesions stained somewhat lighter than normal elastic tissue (with orcein, brownish red or light brown, with the Weigert stain, blue-gray), but they were in direct continuity with the elastic fibers of the surrounding tissue. Occasionally similarly altered elastic fibers were seen in the deeper layers of the cutis.

With picric acid contrast staining, the coils and granular masses of the lesions showed a yellow color, or occasionally remained a light brown, like the other elastic fibers of the cutis. With a combination of the elastic tissue skin and the van Gieson stain the connective tissue fibers in the center of the lesions usually stained only a light or yellowish red, while the connective tissue at the periphery was fuchsin red. With van Gieson stain alone the lesions described stained yellow, like elastic tissue; the connective tissue fibers of the cutis stained in different shades of red.

In the layer directly beneath the epidermis, in the midst of the normal tissue, was a stratum, staining intensively with elastin stains, which was composed of variously shaped bodies, sometimes U-shaped, sometimes coiled or spiral. In many cases these were directly continuous with the fine elastic fibers of the surrounding tissue; in other cases they showed no relationship to these fibers, but on section looked like enlarged and misshaped elastic fibers.

Dubendorfer's[5] *Case.*—Dubendorfer reported the following case in a 7-year old boy who came for treatment for a slight psoriasis. In the left upper gluteal region there were several irregular rounded spots the size of the palm of the

5. Dubendorfer: Ueber "Pseudoxanthoma elasticum" und "Colloide Degeneration in Narben," Arch. f. Dermat. u. Syph. **64**:175, 1903 (one colored plate of histology).

hand and more numerous raised bands and spots. The latter were on the average 1 cm. long and from 0.25 to 0.5 cm. wide. The surface structure of the skin was normal. No psoriasis lesions were found in this region. The bands were only slightly raised. They were sometimes parallel to each other, sometimes confluent, forming a widemeshed network. When the surrounding skin was hyperemic, they were often difficult to distinguish clearly. They disappeared into the deeper layers of the cutis, showing a yellowish tinge through the cutis. On pressure, a slight elevation under the cutis was felt and on heavier pressure a slight resistance was noticeable. There were no subjective symptoms. The lesions did not change in the several weeks that the patient was under observation. The yellowish color of these lesions was the most noticeable symptom.

An elliptical piece was cut across the long axis of one of the bands, including normal tissue on both sides, fixed in absolute alcohol and mounted in paraffin. With ordinary nuclear stains, only a few changes could be seen. The epithelium and the pars papillaris were normal. Around the vessels, especially around the follicles, there was slight infiltration, mostly of mononuclear leukocytes. There were no signs of inflammation. Much more evident changes were noted with elastic tissue stains, both with orcein and Weigert's stain. With a low power, sharply circumscribed lesions were seen in which the deeply stained elastic tissue fibers appeared in large numbers and in peculiar arrangement; these lesions were situated in the middle and deep layers of the cutis, reaching nearly to the subcutaneous tissue. They had no relation with the vessels, the follicles, or the sweat glands. The cutis lying between the lesions appeared absolutely normal as regards both the elastic and the collagenic tissue.

With the high power microscope the center of these lesions was shown to be formed of deeply stained elastic tissue—no longer in normal fibers, but either in numerous fragments or in bands of unusual width and irregular contour. Between these, only collagen tissue was seen. On closer examination it was seen that the intensity of the stain varied, and in some locations, small dark nuclei were seen within the bands. On the periphery of the lesions it could be seen that these fragments and bands were the continuation of elastic fibers, which were, however, swollen and irregular in outline. In some instances, however, the transition to normal elastic fibers appeared to be more sudden. Outside the lesions, also, the elastic fibers appeared somewhat abnormal, less sharply outlined than usual, irregular and knobby in outline and splitting at the ends.

Staining showed the collagen tissue to be normal.

Werther's[6] *Case.*—Werther reported the case of a woman aged 28, who stated that two of her sisters had had the same kind of skin lesions. The patient had chronic stomach trouble, for which she was dieting regularly. She appeared pale and weak; her appetite was poor. The lungs were normal. The urine showed neither sugar nor albumin. The skin lesions were most numerous around the neck, extending from the hair line downward and forward to the clavicle, and behind to the spines of the scapulae. Lesions were also found in the anterior axillary folds and at the elbow joint. The lesions were raised from 2 to 3 mm. above the skin surface. The color was that of ivory, with a slightly bluish tinge. On the neck the lesions were confluent, forming an irregular network. On the edges of this lesion and elsewhere where the lesions were less marked there were separate rounded papules. The surface was smooth, and

6. Werther: Ueber Pseudoxanthoma elasticum, Arch. f. Dermat. u. Syph. **69**:23, 1904 (one clinical stereoscopic picture and two colored histologic plates).

the consistency soft. The skin surrounding these papules had a peculiar glistening appearance. The skin lacked the normal elasticity, especially around the neck lesions. There was only a mild itching. The lesions were first noted when the patient was 16 years old. They had increased gradually since that time. During the three months that the patient was under observation no change could be noted.

A piece was removed from the edge of one of the lesions. Sections were prepared as follows: (1) in glycerine, unstained; (2) stained with hematoxylin and eosin; (3) van Gieson stain; (4) Wiegert stain; (5) Unna-Taenzer stain-orcein and methylene blue; (6) elastic tissue stain by Unna's method (orcein, polychrome methylene blue and orange-tannin solution).

The examination showed a normal epidermis, and the pars papillaris flattened or stretched. The subpapillary blood vessels were prominent because surrounded by new connective tissue. The connective tissue bundles of the derma immediately beneath the epidermis showed their regular normal arrangement. The elastic fibers showed their normal fineness, running horizontally in the lower strata and extending upward into the epidermis.

In the layers of the derma, there was a region of the abnormal structure evident even in the unstained sections. This region was sharply defined and never extended into the subcutaneous tissue. This region, in the unstained preparation, was filled with irregular granulated, knotted bundles, which, with the lower power lens, were seen to be closely packed together and showed an irregular refraction of light. In this region lay the characteristic lesions which clinically appeared as yellowish raised papules. This region stained intensively with eosin and showed fewer interstices than the surrounding layers. The connective tissue nuclei were increased. With the high power lens it was seen that the eosin stained collagen bundles were irregular in arrangement and in outline. Between the collagen bundles was a granulated mass that stained less intensively with eosin and in some sections diffusely with hematoxylin. The exact nature of this mass could not be determined with these stains.

With the van Gieson stain and the low power microscope the actual lesion showed larger spaces between the collagen bundles, which stained fuchsin red, than the region around them. They were seen to be filled with material that stained with picric acid so that the yellow overshadowed the red. With the high power lens this yellow tissue was seen to be, not homogeneous, but granular or cloudy, and occasionally showed nuclear staining properties (brown in this case), hence basophilic characteristics.

It is evident that the elastic fibers, which stained slightly with eosin and with the picric acid of the van Gieson stain, were chiefly responsible for the clinical lesions, and that this tissue differed somewhat in chemical and physical characteristics from the normal. The connective tissue was also involved but to a lesser degree.

The specific elastic tissue stains, according to the Weigert and Unna methods, showed the changes more clearly. With a low power lens, the elastic fibers above and below the lesion were seen to be as fine as normal, of even outline, and regular arrangement. In the affected region, however, a normal regular fiber was rarely seen. Here there was an irregular arrangement of swollen, granular coils. As a rule, this tissue stained less intensively with orcein than normal elastic tissue. With the Weigert stain the difference was less marked.

With a more powerful microscope, with either stain, the transition stage between normal and abnormal tissue was more clearly seen. The normal fibers first became thicker and undulating in outline, with numerous constrictions

though without actual segmentation. Occasionally, they showed a segment that did not stain—a picture that resembled a mycelium. The arrangement of these fibers also was more irregular than the normal, and the ends were either brushlike or knotted. Here also some nuclear staining tissue was evident. Between the fibers and the fiber fragments were numerous cells which were of the general type of connective tissue cells, though varying somewhat from the normal. With polychrome methylene blue, mast cells were seen in the lesions and the immediate surrounding region. There were no giant cells. The use of the Unna "elastic-elagin" stain showed a blue reaction in the diseased tissue, while normal tissue showed a light brown orcein color. The change from staining to nonstaining segments was also shown.

Gutmann's[7] *Case.*—Gutmann had under his care a woman 23½ years old, with chlorosis and constitutional syphilis. Her face was much freckled and her neck somewhat so. In addition, a skin affection was noted on the neck, consisting of whitish or yellowish slightly raised plaques, over which lay the normal epidermis. They felt harder than the normal skin. Where the lesions were most numerous, they were arranged in rows, sometimes forming a narrow network, in the interstices of which were slightly livid fossulae. The most numerous lesions were on the sides of the neck, extending upward and backward to the hair. Lesions were also noted in front on the throat, though less numerous. The patient stated that these lesions had been noticed since childhood (as long as she could remember) and that a sister and a brother had had a similar affection, also since childhood. She could not say whether the parents or any other members of the family had been affected.

Microscopic examination showed the following: The epidermis was entirely normal. The pars papillaris showed many yellowish, granular cells, and free pigment, also cellular infiltration, especially around the vessels, mostly lymphocytes. Many mast cells were noted in the pars papillaris and also in the adjacent parts of the cutis. In the cutis, the cellular infiltration was less marked, the collagen tissue and the elastic fibers were normal in the pars papillaris and the adjacent section of the cutis. The middle and deep layers of the cutis, with nuclear stain, and sometimes with hematoxylin, were seen to be filled with bluish violet coils and clumps (sections fixed in absolute alcohol). The pathologic process was sharply separated from the upper layer of the cutis above and from the subcutaneous tissue below, reaching nearly to the level of the sweat glands. In some cases the lesion was related to a hair follicle or sebaceous gland in such a way that a typical section of a single lesion was a rectangle with its long side parallel to the subcutaneous tissue and its short side formed by the follicle. The follicles were entirely normal, except for occasional cellular infiltration. Sections of the bandlike lesions showed a pathologic process covering the length of an entire section of the deeper layers of the cutis and about three fourths of its width. Staining with the Weigert and the Unna-Taenzer stains showed that this tissue was made up of altered elastic fibers, which stained somewhat less intensively than normal fibers. The fibers had become irregular masses and coils. Sometimes they appeared widened and spiral or corkscrew-like; sometimes a narrow band that stained a dark brown bordered a gray or light brown center, filled with numerous dark staining nuclei. Often one part of a fiber would show a dark stain, the next a lighter shade, or a fiber would be repeatedly segmented transversely. Sometimes the

7. Gutmann: Ueber Pseudoxanthoma elasticum (Darier), Arch. f. Dermat. u. Syph. **75**:318, 1905 (one colored histologic plate).

end of a fiber would be knotted and sometimes brushlike. On the periphery of the lesion, transition forms of the elastic fibers could be demonstrated, showing clearly the change from the normal to the pathologic type. The elacin reaction was negative. In sections fixed in alcohol and stained with the van Gieson stain, the pathologic elastic fibers sometimes showed a peculiar brown violet color.

Collagen tissue was plentiful in the lesions. The trabeculae were somewhat thicker and coarser than usual, otherwise the specimen was normal both in color and in staining reactions.

Cellular infiltration was only occasionally seen in the plaque, and then only around the vessels or the sweat glands. In some sections there was a noticeable increase in connective tissue cells and also scattered giant cells in considerable numbers. Their relation to the altered elastic fibers was not clear. With suitable stains, no fat could be seen within the lesions and naturally no xanthoma cells.

Dohi's[8] *Case.*—Dohi's patient was a woman aged 74 years. In her youth she had had acne of the face. In later years, she had had an epithelioma of the nose between the two eyebrows, cured by radium. The skin lesions under discussion began many years before—according to the patient's statement—probably twenty years or more. None of her relatives had had any similar lesions. There was no subcutaneous symptoms. Numerous raised lesions, varying in size from that of a pinhead to that of a lentil, round or irregular in outline, were found on the forehead, eyelids, cheeks, upper lip and chin. Their surface was smooth and flat. These lesions showed a xanthoma-like coloring—straw yellow to yellowish brown—and felt harder than the normal skin. Their arrangement was symmetrical. Sometimes they were isolated, sometimes confluent, forming an irregular network. The skin between them appeared normal. The eyelids showed only isolated efflorescences. The scar of the healed epithelioma was visible. There were numerous freckles on the face, hands and forearms.

A piece of the diseased skin was excised from the right cheek, and fixed in absolute alcohol. Sections were mounted in both celloidin and paraffin, and stained in the ordinary way.

The epidermis was normal and only in a few places was it thinner than usual. There was a considerable accumulation of yellowish brown pigment in the basal layer. In the upper layer of the cutis there were a few pigmented round or spindle-shaped cells. The papillae were flattened.

With van Gieson's or Hansen's stains, the cutis appeared to be divided into three distinct layers, which with a low power microscope were sharply defined. With a stronger microscope the transition from one to the other was seen to be more gradual.

The upper zone, nearest the epidermis, showed regular rose colored connective tissue fibers running horizontally. The subpapillary blood vessels and lymph spaces were normal. Next came a wider, less compact zone which was made up of irregular yellowish brown clumps. In this zone were several connective tissue fibers or bundles running horizontally or obliquely, sometimes appearing to connect the upper with the lower zone. The lowest zone was the widest,

8. Dohi: Ueber "Pseudoxanthoma elasticum" and ueber "Kolloide degeneration" der Haut, Arch. f. Dermat. u. Syph. **84**:179, 1907 (one histologic plate and two colored figures).

occupying almost two thirds of the entire cutis. The connective tissue bundles usually were horizontal and stained rose red with acid fuchsin. With the stronger power lens, yellowish brown clumps or granular masses were seen between the collagen bundles, especially in the borderline between the middle and the lower zones. The sweat glands and hair follicles lay in the lower zone.

With nuclear stains without contrast staining with acids, blue-violet granular clumps showing affinity for basic stains were seen in the middle zone. The three zones described were less clearly defined than with the van Gieson or Hansen stains. The nuclei of the connective cells were somewhat increased in number in the sharply defined lesions and in the tissue around them. There was slight round cell infiltration in the middle zone of the cutis and a thin layer of round cells around the hair follicles, sweat glands and blood vessels. Mast cells were also increased, especially around the vessels, and in the round cell infiltration of the deeper layer of the cutis.

The findings with the elastic tissue stains, according to the Weigert or Unna-Taenger methods, were much more remarkable. Even with the naked eye, a sharply defined dark area could be seen under the epidermis. With the low power microscope, bandlike irregular granular or clumpy masses were visible in the upper part of the cutis, corresponding to the middle zone in the van Gieson stain preparations. They stained dark brown or almost black with either the Unna-Taenzer or Weigert stain, very much like normal elastic fibers, only more intensely in certain regions. This zone covered from a fourth to a half of the cutis and was separated from the epidermis by a narrow, lighter zone. Toward the sides this zone grew smaller; sometimes hair follicles and excretory ducts of the sweat glands formed its boundaries. With a stronger power of the microscope more marked changes were visible. The elastic fibers lost their regular outlines. They were sometimes swollen, sometimes indented, sometimes broken transversely or twined into a network. Often they showed knotty swellings at the end. Sometimes a number of fibers met in a rosary-like formation. The fibers were sometimes straight, sometimes U-shaped, sometimes spiral. Sometimes only a small edge of the fibers stained intensively—black or dark brown, the inner portion being only gray or light brown. Sometimes also there were more or less numerous dark colored nuclei, or vacuole-like lighter spaces. With special elastic tissue stains followed by staining with carmin or polychrome methylene blue, round, spindle-shaped or irregular connective tissue cells, staining normally, and a few mast cells were seen between these altered fibers; with carmin or picric acid stain a small number of red or yellow staining connective tissue bundles were seen. In the upper zone, immediately below the epidermis, which lay over the chief lesions, the elastic fibers were mostly of normal fineness and thickness, running horizontally or with the upper fibers extending upward to the basal cells. Sometimes their number was much diminished, and sometimes they were entirely lacking.

In the lower zone, including the lower half or third of the cutis, the elastic fibers sometimes were parallel to each other, forming bundles, and sometimes woven into a network, but showing normal contour and fineness and normal chemical reactions. By closer observation, it could be seen that the altered fragments extended down into the deeper layer of the cutis to the level of the sweat glands. At the boundary of the lesions the transition from normal elastic fibers to the abnormal fragments could be distinguished, but there was usually a fairly sharp boundary line.

Unna's elacin stain showed a limited number of fiber fragments in the center of the lesions that stained blue or red. Otherwise this stain gave no reaction.

The collagen tissue in the lesions was diminished and atrophied, but its staining reaction and its relation to the elastic tissue masses were normal. It stained well with fuchsin or eosin.

Neither giant cells nor hyaline degeneration was seen. The vessels of the cutis showed no degeneration or thickening of the walls, but occasionally the capillaries showed projecting endothelium in the lumen.

Little's[9] *Case.*—Little reported a case of pseudoxanthoma elasticum of Balzer in a woman aged 56 years. The eruption consisted of meshlike patches of buff-colored infiltration, lumpy in some places, in others linear and hardly at all raised from the surface; the whole of the neck was occupied by the eruption, but it was especially marked at the sides. The face was entirely free. Small patches of the same type were present in the flexures of the elbow. The condition had persisted for more than twenty years, and there were no symptoms in connection with it. The patient had never had jaundice or liver troubles.

The exhibitor had had two cases, of much more limited distribution of pseudoxanthoma elasticum, in which a biopsy had corroborated the diagnosis; this had not been obtainable in the present instance, but the clinical similarity of the case now shown with these two made this diagnosis more than probable. In Brocq's recent treatise the statement was made that only four cases had hitherto been recorded: one by Balzer, one by Chauffard and Darier, one by Bodin, and one by Werther. This remained, therefore, one of the rarest of skin diseases; but probably the difficulty of diagnosis without a biopsy and the impossibility of obtaining this in many instances added to the obscurity of the disease and the rarity of its identification.

Bosellini's[10] *Case.*—Bosellini reported a case in a woman aged 45 years. There was no history of past disease. According to the patient, the present skin lesions were six or seven years old; the disease had begun as two or three spots on the forehead, and had advanced slowly. At the time of the examination, the dermatosis covered the entire width of the forehead and extended slightly over the roof of the nose and over the cheeks. The elements were symmetrically arranged raised lesions, the size varying from that of a millet seed to that of a hemp seed, lying in racemose groups, and resembling herpes. They were very close together, but always separated by regular grooves. The small groups were found in the folds of the forehead; the grooves within these groups ran horizontally. Vertical grooves with normal skin divided the groups from each other. The elements were smooth, glossy and dark brown or lead color. There was no inflammatory reaction and no desquamation. The dermatosis was also found on both hands, following the radial side of the index finger and the ulnar side of the thumb in a continuous line. Here the individual elements were not so definitely separated and the lesions resembled nevus-like bands.

A small piece of skin from the right side of the forehead was excised, fixed in alcohol and Zenker's fluid, and mounted in paraffin. Several common stains were used with the different sections—for the normal elastic tissue, orcein; for the altered elastic tissue, Unna's polychrome methylene blue and tannin; for the collagen, orange-tannin. In addition to these stains, other nuclear stains were used, especially van Gieson's and Pappenheim's.

The epidermis of the individual lesions, as well as the grooves between them, appeared normal, except that the layers over the lesions were fewer in number.

---

9. Little: Case Presentation, Brit. J. Dermat. **20**:194, 1908 (author mentions having had two other cases).

10. Bosellini: Pseudoxanthoma elasticum, Arch. f. Dermat. u. Syph. **95**:1, 1909.

There was an abundance of pigment in the basal layer and also in the layer above it; also some vacuolation of the basal layer with displacement of the malpighian cells.

The papillae had disappeared from the pars papillaris, leaving only a connective tissue layer. The staining reactions of the collagen and the elastic fibers of this layer were normal. The layer below the pars papillaris showed no special characteristics and was, in fact, largely absorbed by the latter.

The greatest change was seen in the middle layer of the cutis. With the low power microscope, numerous round foci were seen extending upward. They were imbedded in a diffusely altered tissue, the pathologic changes in both being of much the same character. The elastic tissue in this layer was unusually plentiful between the collagen bundles, and showed a marked basophilic reaction. This made a clear demarcation between the middle and the deep layer of the cutis. The elastic tissue of the deep layer showed an intensive reaction to the orcein stain, but the elastic fibers of the middle layer stained only slightly. If thionin was added to the orcein to produce a nuclear stain, the elastic tissue of the middle layer showed a marked basophilic reaction, which was also obtained with methylene blue and tannin, while these stains gave no reaction in the elastic tissue of the deep layers of the cutis or of the pars papillaris. The elacin showed similar reactions. The collagen bundles were entirely normal in morphology, arrangement and staining reactions.

Considering the single foci, it was evident that they were not all alike. The smallest were composed of a thick feltwork of regular, well developed, clearly defined elastic fibers, with a basophilic reaction. The upper part of these lesions was more compact than the lower, where the fibers showed their continuity with the basophilic fibers of the surrounding cutis. The collagen in these elastic coils was somewhat reduced. There were few connective tissue cells.

Besides these small elastoma, there were larger round or oval lesions in which the elastic tissue predominated, and still larger and more developed lesions composed of collagen chiefly, with a trace of elastin. Above these lesions was a lymph space which separated them almost completely from the pars papillaris. Around the lesions were numerous mast cells, and around the blood vessels considerable cellular infiltration was present but no sign of inflammation.

With the Zenker stain, the lesions showed no special characteristics, but were clearly brought out. With a stain combining polychrome methylene blue, orange and orcein, it could be clearly seen how the elastic fibers were broken up between the collagen bundles, showing granular degeneration, and how the collagen without infiltrating them, gradually covered them.

Pinkus'[11] *Case.*—At a meeting of the Berlin dematologische Gesellschaft, March 8, 1910, Pinkus presented the case of a woman, 53 years old, with lesions of pseudoxanthoma elasticum similar in extent to those in the cases of Darier and others. The axillae, the elbows, the region of the navel, the inguinal folds and the neighboring parts of the trunk and the thighs, and, to a lesser extent, the knees, showed lesions. Around the neck, like a band, was a scarred area with contracted skin, in which were the yellow papules of pseudoxanthoma. The folds of skin at the axillae and the groin were exaggerated, and the skin was leathery. The patient was very thin and appeared as if her skin was too large for her. Microscopically the yellow papules contained disintegrating elastic

11. Pinkus: Case Report, Arch. f. Dermat. u. Syph. **104**:94, 1910.

fibers of poor staining reaction, appearing as if only a sheath (and not always intact) was left from which the elastic contents had been extracted.

Little and Sequeira's[12] *Case.*—Little and Sequeira reported a case of pseudoxanthoma elasticum. The patient had been seen by Dr. Little at St. Mary's Hospital about seven years ago, when she was about 12 years of age, and was subsequently shown to the Dermatological Society of London. The clinical appearance had not changed appreciably in the interval. She had now come up to Dr. Sequeira's clinic for treatment. A section of the skin was obtained by Dr. Little seven years ago, and the specimen exhibited at the meeting showed the characteristic appearances of the disease as described by Balzer, Darier and others. The elastic tissue seemed to form the bulk of the tumor; it was greatly increased in quantity and was swollen and broken up into fragments and granular débris which occupied the corium below the papillary zone.

The president of the society said he remembered that many years ago Sir Malcolm Morris asked him to go and see two sisters from Ireland, in whom the diagnosis of pseudoxanthoma elasticum of the neck was made. Their condition looked exactly like that in the present case.

Herxheimer and Hell's[13] *Case.*—Herxheimer and Hell describe a rather exceptional case of pseudoxanthoma elasticum occurring in a boy 16 years old, who had always been in good health, who came for treatment of a weeping eczema, which healed in a few weeks. A skin lesion was noted on the face which had existed since birth, but which had caused no symptoms. None of the family showed similar lesions.

The lesions were symmetrically arranged on both cheeks, on both eyes, upward along the side of the eyes and downward to the corners of the mouth. The upper border was sharply defined; at the side and lower edge, the transition to normal skin was gradual. The lesions were made up of small trabeculae, with spaces not larger than a pinhead between them, forming a regular small network. The lesion had a duller appearance than the normal skin and was rough and uneven to the touch. Otherwise there was no alteration in the consistency. The elasticity of the skin appeared normal.

The patient was small but in good health and strong. A physical examination and urinary tests revealed nothing abnormal.

A piece of the lesion was excised from the left cheek, fixed in liquor formeldelydi and alcohol. Sections were mounted in paraffin. Microscopic examination showed the following:

With a hematoxylin-eosin stain the epidermis showed an irregular surface and was thinner than normal, with only 3 to 4 cell layers. The surface capillaries were slightly widened. In the connective tissue, there was some lymphocyte infiltration around the vessels. Where the atrophy of the epidermis and the rete was most marked, there were circumscribed lesions staining pale rose, usually round and almost entirely without nuclei. These lay under the epidermis, in the region of the pars papillaris, with the epidermis apparently arched over them.

With a cresol-violet stain the same morphology as in the foregoing was shown. The epidermis and connective tissue showed the normal violet shade.

12. Little and Sequeira: Case Presentation, Brit. J. Dermat. **22**:131, 1910; note by Calcott Fox—two sisters in Ireland had been seen by him.

13. Herxheimer and Hell: Eine Beitrag zur Kenntniss des Pseudoxanthoma elasticum, Arch. f. Dermat. u. Syph. **111**:761, 1912 (two histologic figures).

The circumscribed lesions noted with the hematoxylin-eosin stain showed sometimes a darker and sometimes a lighter shade, and were sharply marked off from the surrounding tissue. These small lesions never extended to the basal layer of the epidermis, as there was always a narrow unstained zone between. With the high power microscope, these lesions were seen to be made up of a thick, tangled maze of apparently regular fibers, some thin, some thicker, irregularly intertwined. Sometimes the mass was not so thick or so clearly defined, and the fibers were less intensely stained.

With carmin-lithium-carbonate and with the van Gieson stain, these lesions appeared very pale; with hematoxylin-eosin stain, steel blue; with Unna's universal stain, brown; with the Unna-Taenzer stain, reddish brown; with Unna's elacin stain, brownish red, single fibers in the vicinity, brownish blue. With these stains the single fibers were clearly visible, and the lesions were sharply distinguished from the surrounding tissue.

With Wiegert's stain, the elastic fibers of these lesions, staining a bluish-black, were clearly distinguished. In some places the single fibers were abnormally thickened and swollen. The transition from normal elastic fibers could also be seen.

The fourfold stain of Frenkel showed the epidermis yellow, the connective tissue dark green, and the pathologic lesions reddish brown. With a high power microscope the single elastic fibers were seen, with a few green connective tissue fibers among them, especially on the borders of the lesions.

Concerning the etiology of the condition, Herxheimer and Hell express the opinion that this is unknown.

Kingbury and Heimann's[14] *Case.*—A girl, 21 years of age, born in England, who had been living in the United States for the past six months, had lesions which had been present on the sides of the neck for five years. They were rounded or oval, slightly elevated, buff colored patches about a half inch in width. Urinalysis two months ago showed 0.92 glucose. Two subsequent examinations were negative.

The microscopic examination showed that the epidermis was normal, as was the contour of the papillary body. The collagen was swollen at all levels, and there was a slight numerical increase of the fibroblasts. Vessels were not increased in number but were slightly dilated, without being engorged. Their endothelial lining was somewhat swollen, and outside a few vessels was a trifling infiltration consisting entirely of fibroblasts, arranged in one or two concentric rows. The most significant changes appeared in the elastic tissue, which was fragmented, curled back and formed in clumps of disrupted fibrils, or found isolated in broken strands. Some of the fibers stained blue with Unna's polychrome methylene blue dye. No plasma cells, giant or xanthoma cells were found.

Mito's[15] *Case.*—About six years ago an otherwise healthy woman, 27 years old, without any subjective symptoms, noticed small, round, slightly raised hard spots with yellow to brown coloring on the neck, in the axillae and about the navel. Sometimes these small spots ran together. In between the skin seemed normal. In the middle cutis was a dark colored focus, which microscopically

14. Kingsbury and Heimann: Case for Diagnosis (Yellow Lesions on Neck), J. Cutan. Dis. **34**:377, 1916.

15. Mito: Ein Fall von Pseudoxanthoma elasticum, Japan. Ztschr. f. Dermat. u. Urol. **20**: No. 2, 1920.

TABLE 1.—Case Reports of Chronologic Order

Author	Year Reported	Case No.	Age	Sex	Nationality	Duration	Subjective Symptoms	Localization	Color	Clinical Picture	Site of Histologic Change	Histologic Picture	Complications	Remarks
Balzer..... ..	1884	1	49	M	French	Since childhood; was more marked	Mild itch in beginning	Neck, axillae, elbows, navel, less at inguinal and popliteal regions	Pale yellow	Flat xanthelasmatic plaques 1 sq. cm. to 1 sq. mm.; long axis with skin folds; forms small elevations	.....	Hypertrophy of elastic tissue; fibers loosened, broken, knotty, wreath-like; often binding of destroyed and healthy fibers; little fat and few xanthelasmatic cells in modified skin	Formerly malaria; now pulmonary tuberculosis	At necropsy, same kind of spots found on endocardium and myocardium as on skin
Darier, also Chaffard, also Besnier and Doyen, also Hallopeau and Lafitte	1896	2	42	M	French	16 years; for 7 years somewhat larger	Tender to touch	Symmetrical on neck, clavicular regions, axillae, elbow, abdomen, especially below navel, groin, undersurface of penis, anal cleft and popliteal space; small lesions on upper lip, mucosa of lip and cheek and palpebral commissure	In beginning bluish, now yellow like café-au-lait	Xanthoma-like spots and plaques, hardly elevated, 5 cm. broad and 10 cm. long; slightly uneven and made up of hemp to lentil sized spots; skin soft and pasty like moist velvet, slightly elastic; at periphery, small yellow or white plaques	Entire depth of cutis	Rounded off, not sharply limited lobes or coils showing laceration, swelling, disintegration of increased elastic tissue even to crumbling (elastoclasia, elastorrhexis); elastic tissue inclines toward basophilia; connective tissue almost normal; connective tissue cells increased at site of elastoclasia	Typhoid at 23; alcoholic gastritis; icterus; now pulmonary tuberculosis	Small healthy strips present between epidermis and affection on mucosa of mouth; identity of yellow spots on palpebral commissures with the remainder not clearly evidenced
Bodin.....	1900	3	50	M	French	30 years; after some years increased	None	Symmetrical on lower abdomen, clavicular and axillary regions, inner surface of arms and genitocrural regions	Faded yellow	Round or oval pinhead to lentil sized, individual, grouped, or confluent papules forming plaques	Middle layer of cutis	Papillary bodies somewhat flattened; new perivascular infiltration; elastic tissue split, twisted, forming crumbling masses connected with healthy tissue; connective tissue bundles crowding one another; volume increased	Digestive disturbance; diarrhea; urine negative for sugar; phthisis	Innumerable multinuclear giant cells (Bodin cells) especially in periphery of masses about vessels
Von Tannenhain	1901	4	74	F	German	.....	.....	Anterior surface of upper arms, upper calves, about crests of ilium, less under chin and side of breasts	Opaque and yellowish	Irregular millet seed sized papules, some forming plaques; infiltration evident	Upper cutis	Flattened papillary body, roughly limited oval masses in them; swelling; separation into fibers; rolling together of elastic fibers; in part, granular disintegration; connection of diseased with healthy tissue; connective tissue trabeculae greatly swollen and becoming homogenized	Arteriosclerosis; endocarditis and myocarditis; senile marasmus; pneumonia; intestinal hemorrhages	Calcification and formation of hyaline layer found at necropsy as secondary findings
Dubendorfer	1903	5	7	M	German	.....	None	Left upper gluteal region unsymmetrical	Faint yellow	Palm sized flat elongated stripes and spots 1 by ¼ to ½ cm., sharply circumscribed and slightly elevated; meshy network indicated; minimal resistance	Middle and deep layer of cutis	Irregularly swollen and contused elastic bundles and broad bands; between them only collagen tissue; transition into healthy bundles; collection of cells about vessels and follicles	Mild psoriasis	Numerous mast cells; not accepted by all as case of pseudoxanthoma elasticum

TABLE 1.—Case Résumé in Chronological Order—(*Continued*)

Author	Year Reported	Case No.	Age	Sex	Nationality	Duration	Subjective Symptoms	Localization	Color	Clinical Picture	Site of Histologic Change	Histologic Picture	Complications	Remarks
Werther.....	1904	6	26	F	Irish	12 years; very little increase	Mild itching	Neck anterior axillary folds and elbows	Ivory color with light bluish tone	2 to 3 mm. round, smooth, soft papules, many running together to an irregular nest; little elasticity of skin	Middle and deep cutis	Swelling and orderly lapse of elastic bundles; disintegration of same (as if septums had formed) partly basophilic reaction; collagen trabeculate thick and swollen with proliferation of nuclei; marked increase of endothelial lining of small blood vessels	Chronic gastritis; freckles on face; chloasma	2 of 5 brothers and sisters have same affection since 18 years old; same localization; incised wound led to keloid; innumerable mast cells in lesion
Gutmann....	1905	7	28	F	German	Earliest childhood	.....	Entire circumference of neck	Whitish to ivory color	Plaques, single or in rows, confluent into a narrow nest; firmer than surrounding skin	Middle and deep layer of cutis	Epidermis thinned in places; papillary bodies flattened; transition into healthy tissue from clumpy masses of swollen, disorderly, knoblike, distended, partly fragmented or granulated broken-up elastic bundles demonstrated; elacin not clearly demonstrated; collagen tissue in lesion decreased	Chancroid between eyes; freckles on face, arms and hands	
Dohi....	1907	8	74	F	German	20 years	None	Symmetrical; forehead, eyelid, cheek, upper lip and chin	Straw yellow to yellowish brown	Pinhead to lentil sized flat, smooth, sharply marginated elevations, somewhat harder than normal skin, either isolated or fused into network	Middle and deep layer of cutis	Coil and clump formation of elastic bundles, which are swollen and ligament-like; elacin reaction negative; connective tissue trabeculae somewhat coarser than normal; otherwise connective tissue unchanged	Chorosis; freckles; macular syphilid	1 brother and 1 sister have had same disease since early childhood; isolated giant cells present
Little.... ..	1908	9	56	F	English	20 years	None	Whole neck, flexures of elbows	Buff color	Meshlike patch of buff-colored infiltrations, lumpy in places, in others linear and hardly raised from surface	No biopsy reported			
Boselini.....	1909	10	45	F	Italian	6 to 7 years on forehead; 3 to 4 years on hands	None	Symmetrical; forehead, and contiguous portions of root of nose and cheek regions, flexor surface of thumb and index fingers (as bands 1 cm. broad)	Slate brown to lead color	Millet seed to hemp seed sized hemispherical, smooth, shiny elevations, arranged like herpetic lesions, separated from each other by regular grooves; on hand verruca-nevoid in form	Middle cutis	Epidermis somewhat and papillae entirely atrophied; round or oval groups of entangled basophilic reacting elastic tissue bundles shown between which collagen fibers are decreased; increase of connective tissue indicates size of lesion; homogeneous compact collagen mass with basophilic reaction (Kollen?); pigment in greased	Pterygium	Mast cells present; (this case not always accepted, but Herxheimer and Hell include it as an example of the disease)

Pinkus.....	1910	11	58? 47?	F	German	.....	.....	Neck, axillae, elbows, navel region, inguinal folds, upper leg, sparse at knees	Yellowish	Arranged in stripes, half circles and circles are pinhead to lentil size papules between which skin is slightly depressed and shiny with light bluish tint; folds of axillae and groins hang pendulous	Deep cutis	Lesions consist of crumbly, curly, interlocking elastic bundles which look like thick decayed partly dissolved elastic bundles, or as if only part of the elastic cortex was left	Tertiary syphilis	Scars on neck probably from acne; lost weight last year; skin of axillae thick as leather and hangs in folds
Little and Sequeira	1910	12	19	F	English	.....	.....	.....	.....	.....	Cutis under papillary bodies	Elastic tissue seemed to form bulk of tumor; greatly increased in quantity, swollen and broken up into fragments or granular débris	... .	No change since seen seven years previously
Herxheimer and Heil	1912	13	16	M	German	Earliest childhood	None	Symmetrical on cheeks	Normal to light pale	Seemingly orderly trellis work of fine trabeculae; between are pinhead sized clear fields	Papillary body	Sharply circumscribed foci made up of thick maze of thickened, apparently orderly, elastic bundles with only occasional transition into normal	Eczema of head	
Kingsbury and Heimann	1916	14	21	F	English	5 years	.....	Sides of neck.....	Buff colored	Rounded or oval slightly elevated, about ½ inch in width	All levels	Collagen swollen; slight increase of fibroblasts; elastic tissue fragmented, curled back and formed in clumps of disrupted fibrils or isolated in broken strands; no plasma, giant or xanthoma cells	.....	One urine examination; 0.92 glucose; two other examinations negative
Mito.....	1920	15	27	F	Japanese	6 years	None	Neck, axillae and navel region	Yellow to brown	Pinhead to linseed size round slightly raised hard spots with smooth yellow to brownish coloring which sometimes ran together; in between skin normal	Middle cutis	Thick, bandlike, disorderly, broken, clumpy or crumbled bundles; about the neighborhood of lesion, one could distinguish transition of bundles into elastica; xanthoma cells not found	Healthy	
Our case.....	1921	16	39	F	American	35 years	None	Symmetrical; neck, axillae, flexor surface of arms and forearms	Fresh butter yellow	Yellowish small papular elements, individual and confluent, or massed into plaques; grossly thickened skin where lesions exist; exaggeration of normal creases and reduplication of normal folds	Lower and middle derma	Clumps of swollen and degenerated elastic fibers with basic degeneration of collagen fibers in lesions; little change in pars papillaris of derma; sweat and sebaceous glands and hair follicles not involved; no giant or xanthoma cells	Enlarged mediastinal glands	One sister had similar condition; died at age of 34 of tuberculosis

showed many thick bandlike disorderly broken clumpy or crumbled bundles. About the neighborhood of these foci, one could distinguish the transition of these bundles into normal elastica. Xanthoma cells were not found.

ETIOLOGY

Age.—In the fourteen reported cases in which the ages of the patients are noted, they have varied from 7 years, the youngest, to 74 years, the oldest.

Sex.—There has been a preponderance of female cases. Of the 20 cases (those reported and those only mentioned) in which the sex is given, six have been males and fourteen have been females.

Nationality.—There have been six cases reported in full from Germany, and in addition, two other patients have been mentioned who were German. One case in a native of Ireland has been reported in full, and mention has been made in the literature of four others. Three patients were French, three English, and one each were from Italy and Japan. Our case was that of an American woman of German parentage.

Associated Diseases.—Three of the reported cases were in patients with pulmonary tuberculosis. Our patient presented findings which led to the belief that she may have had tuberculosis, which at this time is inactive. The sister of our patient, who had the same disease, died of pulmonary tuberculosis. One patient is reported as showing a secondary macular syphilid, and another patient had a concomitant tertiary syphilid. Gastritis is mentioned three times as an associated disease. Two of the patients had freckles, and one had superficial epitheliomas. A list of the other diseases which were found includes: pterygium, arteriosclerosis, myocarditis, pneumonia, psoriasis and eczema. Except for the tuberculosis, no claim for causal or distant relation has been advanced. One patient, in addition to ours showed a slight transient glycosuria.

Familial Characters.—In two of the reported cases, two other members of the family had the same condition, which became apparent when the same age was reached. Colcott Fox, in the discussion of Little's case, mentioned that he had once been called to see two sisters who were suffering with the affection. A sister of our patient had the same character of eruption. In both sisters it appeared when they were each 4 years old.

Age of Onset.—The age of the onset is given as since earliest childhood or since childhood in four cases. In eight others, the age of the onset is given as: 10, 16, 18, 20, 38, 46 and 54. In our patient and in her sister the onset was at 4 years of age.

Duration.—In the cases reported the duration has been given as four, five, six, seven, twelve, sixteen, twenty, and in one case thirty years. Our patient had the disease thirty-five years. Her sister had the affection for thirty years before she died.

Subjective Symptoms.—In ten reports, subjective symptoms have been mentioned. In eight of these, the absence of subjective symptoms is commented on and in two mild itching is noted.

Color.—In the cases in which color has been reported, the following range has been covered: normal to light pale, whitish to ivory, ivory color with light bluish tinge, yellow to opaque, pale yellow, faint yellow, yellowish, sulphur yellow, yellow like, café au lait, straw yellow, to yellowish brown, yellow to brown and slate brown to lead color. Fresh butter yellow fits the individual lesions of our case and a tawny yellow the flat lesions in the cubital spaces.

TABLE 2.—Location of Pseudoxanthoma Elasticum

Face	8	Ilium	1
Neck	9	Inguinal regions	4
Under chin	2	Gluteal region	1
Clavicular regions	2	Penis	1
Axillae	7	Anus	1
Elbows	5	Upper leg	1
Arms	2	Popliteal spaces	2
Fingers	1	Upper calf	1
Breast	1	Not mentioned	1
Navel	6		

SUMMARY

We have clinically identified a case of pseudoxanthoma elasticum which is one of the rarest dermatoses accepted as an entity. Our case was in a young woman, 39 years of age, who had had the affection since she was 4 years old. Of her circle of relatives, one sister had had a similar condition since she was about 4 years old, and as has been reported for some of the cases, her death was attributed to tuberculosis. Our patient had had a lymph node incised when eighteen months old, and at the present time shows enlarged mediastinal glands on roentgen-ray examination. This is little evidence on which to base a diagnosis of accompanying tuberculosis. The clinical picture in our patient fits that of the published cases. Individual papular butter yellow lesions, with a tendency to confluence, as evidenced by the groups of twos and threes, and the plaque lesions of which there are two varieties, the raised and the flat, have been described for this disease. The folds and exaggerated creases are also part of the accepted clinical manifestations.

Histologically the clinical diagnosis was confirmed. The lower and middle derma showed clumps of swollen and degenerated elastic

fibers with basic degeneration of the collagen fibers in the lesions. This change in the collagen has not been previously thought to be an important change, but in our case it has seemed that the collagen changes are significant. There was little change in the epidermis and the pars papillaris of the derma. Sweat and sebaceous glands and hair follicles were not involved. No giant cells were present and no xanthoma cells.

CONCLUSIONS

1. Pseudoxanthoma elasticum possesses clinical, morphologic and histologic characters that are unlike those of any other known dermatosis. It is, therefore, an entity.

2. The essential clinical features are: yellowish, small papular elements, individual and confluent, or massed into plaques; grossly thickened skin where the lesions exist, although this may not be constant; exaggeration of the normal creases, and reduplication of the normal folds. The neck and the axillae are apparently the sites of predilection.

3. The essential histologic features are: clumps of swollen and degenerated elastic fibers with basic degeneration of the collagen fibers in the lower and middle derma. There is little change in the epidermis and the pars papillaris of the derma. The sweat and sebaceous glands and the hair follicles are not involved. There were no giant or xanthoma cells, although Bodin has found the former.

4. The etiology is unknown. It has been considered a nevus, a form of tumor, and from an association with tuberculosis, as dependent on that disease for its causation. It has been thought to be an idiopathic degeneration, but that does not make the etiology any clearer. It may prove to be dependent on a degeneration of the nerve elements in the situations where the disease exists.

5. One can demonstrate all the characters necessary for a diagnosis. The case clinically identified by us, studied histologically, and here reported, resembles in nearly every respect the classical description of pseudoxanthoma elasticum.

We desire to thank Dr. H. H. Whitehouse for allowing us to report this case. We wish also to express our appreciation of Dr. Elizabeth Finch's [16] kindness in helping in the study and interpretation of the histologic material.

ADDENDA

Since the report given in the foregoing has gone to press, another instance of pseudoxanthoma elasticum has been seen at the New York

16. Dr. Finch died June 21, 1921.

Skin and Cancer Hospital in the service of Dr. A. Schuyler Clark, to whom we are indebted for the privilege of reporting it.

Mrs. M., an Italian woman, 42 years old, came to the dispensary for treatment for psoriasis. The added condition of pseudoxanthoma elasticum was noted during the examination. The patient said that she had first noticed the lesions of pseudoxanthoma when she was about 12 years old. No other member of the family had a similiar disease. The family history was negative for tuberculosis and diabetes mellitus. The patient refused to permit a biopsy, or venipuncture.

The lesions were present in the same regions as on the patient of our more detailed report. Inguinal lesions were also present. The lesions on the neck were practically identical with those of the earlier case. The skin did not hang in folds, and the discrete lesions were more widely distributed, being found over the shoulders. In the axillae and anterior cubital flexures the lesions were similar to those in the first case. No lesions were present on the face.

The patient made only one visit.

STAINING OF SPIROCHAETA PALLIDA BY THE FONTANA-TRIBONDEAU METHOD

ELIMINATION OF HEAT

CESAR FUENTES, M.D.
Of the Calixto García Hospital and the Covadonga Sanatorium Laboratories
HAVANA, CUBA

Our chief purpose in beginning our investigation was to discover a quick and reliable method, which could be employed by any one familiar with microscopic work, to demonstrate *Spirochaeta pallida* in the transudate of a chancre as easily as the tubercle bacillus is demonstrated in the sputum.

Nowadays, as we gain a better knowledge of the invasion of the tissues by the spirochete, when a patient with a so-called second syphilitic incubation is considered to have a possible case of the dreaded nervous involvement, it is convenient for the specialist to have a simple, reliable method to diagnose and to differentiate the chancre. With this in mind we searched for a staining method which should fill these requirements.

Our advocacy of this method does not mean that we consider it superior to the dark-field method, since both methods have their own advantages, but not all laboratories are equipped for dark-field demonstrations.

DIFFERENT METHODS

Giemsa's method, based on the capacity of protozoa to stain with azur or azur derivatives and Levaditi's silver nitrate method are the technics from which many others originated. Among these, the one that seemed best to us on account of its quickness and reliability was Fontana-Tribondeau's.

For this method the following things are needed:

1. A substance to dissolve the hemoglobin in the blood serum from the chancre.
2. Deep fixation.
3. A mordant.
4. Impregnation with silver nitrate without any reducing mixture.

The spirochetes assume a light purple to dark brown color, according to the handling of the technic. This procedure has in its favor the fact that it is quick and reliable; it is possible to stain a specimen in five minutes, and the identification does not take any longer than with any other preparation. As the spirochetes are very delicate organisms it

might be that roughness in the technic through changing their spiral form might be responsible for the many differences often detected in their appearance. This turned our attention to the fact that heat plays a very important part in Tribondeau's technic. In fact, fixation is done by pouring and burning alcohol over the slide. The application of the mordant requires exposure to the flame until it smokes. When the stain is applied it must be kept steaming during a period of thirty seconds.

In our efforts to do away with heat, we tried, first, fixation with burning alcohol. The slides were fixed in the usual way but without using alcohol in the cover glass. Cover glasses cannot stand the heat of the flame without breaking, and as we intended to use them to avoid any silver nitrate stains, as happens with slides, this was another difficulty.

Specimens both with and without alcohol show the spirochetes perfectly. If we keep in mind the fact that the dehemoglobinizing solution serves for fixing just as well, we will realize that a deep fixation is not necessary. Naturally the best proof is found in the result obtained with the controls. As soon as we stopped the use of alcohol, we began to use a cold tannin solution. We made repeated applications during three, four, five and seven minutes, finding that the silver nitrate showed only slightly the desired metallic shade, as there appeared in weak tints red cells, white cells, spirochetes, and other elements of the transudate. We increased the time to ten minutes and we then had satisfactory preparations.

TECHNIC

The preparation of the silver solution includes three steps:

1. Formation of the precipitate.
2. The solution of it with an excess of reagent.
3. Formation of the new precipitate, adding silver nitrate until it turns an opalescent shade.

If more silver solution is poured in, this shade changes to dark brown. If we let it stand, in about an hour there will be at the bottom of the flask a flaky black precipitate and a colorless supernatant fluid; if the precipitate is disturbed it will not lose its flaky character or its staining qualities, but it will have the disadvantage of settling on the slide preparation. After twenty-four hours, it behaves as reported.

In order to find out whether it was essential to heat the silver nitrate solution to stain the spirochetes, controls were made in a cold solution during one, three, and five minutes. Those exposed to the action of the stain for three minutes seemed satisfactory, both the organisms and cell elements appearing well stained, and equaling those submitted to

heat. However, it is fair to add that the reagent was used with an amount of silver nitrate sufficient to form a dark brown solution.

We have stated before that this dark brown color appeared twice, and in order to facilitate its appearance we decided to use a definite quantity of 5 per cent. silver nitrate, and another definite quantity of ammonia, either diluted or undiluted, as this would make the technic more accurate. We took 5 c.c. of silver nitrate and a drop of 50 per cent. ammonia. With this proportion we obtained at once the desired shade. But it seemed as if the diluted ammonia lost its strength, and we decided to use it pure, securing then better results. After studying the action of heat on the morphology of *Spirochaeta pallida,* we have come to the conclusion that the best results are obtained when the reagents are applied cold.

The reagents employed are: glacial acetic acid, 1 c.c., formaldehyd, 2 c.c. and distilled water, 100 c.c.; tannin, 5 per cent., 100 c.c.; silver nitrate, 100 c.c.; ammonia, pure, 10 c.c.

The reagents are used in the following order: Ruge's solution, for several immersions; distilled water; tannin heated until it smokes, and then employed thirty seconds; distilled water; ammoniated silver nitrate precipitate, cold, employed two seconds and in distilled water. Mount in glycerin, using paraffin margins.

CONCLUSIONS[1]

1. Burnt alcohol fixation is not necessary, but is, on the contrary, rather harmful to the morphology of *Spirochaeta pallida.*

2. Ruge's solution is sufficient for fixation and dehemoglobinization.

3. This solution can, however, be substituted by H_2O_2, one-third in water and 1 c. c. formaldehyd, making a volume of 100 c. c.

4. Heat is not essential in order that the tannin may act as a mordant.

5. Fontana's solution may act without heating.

6. The best way to use the method consists in heating tannin until it steams, and applying silver nitrate for one or two minutes.

7. The most typical forms of spirochete are seen when the method is applied cold.

---

1. The staining of Leptospira icteroides, both hot and cold, leads us to the same conclusions.

A COMPARISON OF INGREDIENTS OF RINGWORM CULTURE MEDIUMS

WITH SPECIAL REFERENCE TO AMERICAN AND FRENCH CRUDE MALTOSE *

FRED D. WEIDMAN, M.D.
AND
THOMAS M. McMILLAN, M.D.
PHILADELPHIA

It will be unnecessary to explain the need for the work above indicated to any one who has attempted the culture, particularly the identification of the ringworm fungi. For the sake of others, let it be said, first, that the proposition is very different from the cultivation of the bacteria, and that the difficulties are not along microscopic lines, but preeminently from the gross morphologic standpoint. Yet more precisely, we are not concerned so much with the matter of luxuriance of growth, for at present our fungi grow easily enough. Rather are we trying to coax out differential characteristics. It is with the latter phase that this paper has to deal; but before proceeding to our experimental work some preliminary considerations must be offered to make the work understandable.

The problems before us can best be comprehended by keeping in mind throughout that the molds are plants. Much higher than the bacteria, they consist in most cases not alone of the more vegetative structures, such as the mycelia, which may be compared to stems of plants, but also of reproductive bodies which may be compared to the flowers and fruit. Keeping this in mind, it will at once be appreciated that differences in the medium on which the mold is planted must be expected to produce some order of change in gross morphology, just as variation in the composition of the soil would make a difference in the appearance of a tomato plant. That is, depending on the amount of moisture available, the amount of nutritive substances, such as phosphorus, nitrogen, inorganic salts, etc., we may get anything from a yellow, scrawny, fruitless plant a foot or so high, up to the rank, deep green, fruitful growth with which everybody is familiar. While indulging in this comparison, let us recall that the appearance of plants will be different, too, at different stages of their growth.

---

*From the Laboratory of Dermatological Research, Department of Cutaneous Medicine, University of Pennsylvania.

* Read before the Section on Dermatology and Syphilology at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

All of these considerations hold good for the molds, and as a result we find that their appearance will vary with age, the composition of the medium, its acidity, its moistness, and even the thickness of the stratum on which it is growing. For purposes of identification, therefore, it is necessary that, as a rule, the age of the colony be known (or better the course of its growth be followed from the time it is planted until full maturity), the composition of the medium be precise and the thickness of the stratum be uniform.

MORPHOLOGIC VARIATION

One can better understand why bacteria show less morphologic variation than the molds when one recalls their finer, microscopic

Fig. 1.—Culture Series 1. *Trichophyton effractum;* colonies nine weeks old. First six tubes "all French" ingredients except Tubes 2 and 6 which have American agar; Tube 7, "all French" except for Difco peptone; tubes on bottom row, all American ingredients: first tube, Pfanstiehl maltose; second, Difco; third, Mellin's; fourth, Eflorose; fifth, Dolbey; sixth, Borcherdt's; seventh, Mead's. No acid adjustment. Color and texture were the same on all. The cracks are characteristic on all "all French" tubes, and suggestive on several on the bottom row.

appearance. These more primitive plants consist of cells more dissociated; and the cohesion of the cells, the direction of growth, extension, etc., is therefore more limited than in the case of molds. The latter, having mycelia, can creep outward or upward or interlace with one another, just as vines creep over a rock, or, by becoming more or less compacted and felted together, can lead to a looser or more compact macroscopic appearance, depending on the propensities of the

species. It is this variable, close felting of mycelia which is responsible for the various downy or furry or hairy qualities of different species of mold cultures. Depending on the robustness of the mycelia and the question whether they are entwined into wisps or not, the surface of the colony will appear from delicately downy to coarsely furry.

A further surface feature of the molds is the presence in some species of a powder. An analogous phenomenon does not appear in bacteria because this powder is referable to microscopic-size fructifications of one or another sort (conidia, fuseaux, etc.) which are not produced by bacteria.

The result of all these considerations is that, by way of contrast, a colony of staphylococci, if grown on continually moist agar as we grow our molds, will maintain about the same moist, smooth, glistening

Fig. 2.—Culture Series 1. *Microsporon fulvum;* colonies four weeks old. Tube at left "all French"; at right, Mead's. No acid adjustment. To all intents and purposes they are identical as mycology goes. Illustrates adequacy of several maltoses for this species.

surface over a period of many days or several weeks, whereas a mold will appear materially different. Taking *Microsporon lanosum,* for instance: In the first day or two we see but a few tufts of white down; in the course of a week a coffee-brown powder begins to appear in the center, and a little later this becomes rather extensive. Gradually, during the course of a few weeks more, the powder is overgrown and covered by the down, until by the end of six or eight weeks the colony consists solely of the latter, and has an appearance indistinguishable, in this late stage, from many other fungi.

To go a little further: Suppose the composition of the medium on which our bacterial and fungus colonies were growing were altered in some respect. We should find that in the case of the bacterial growth

a rather radical change would be necessary in order to change the character of the colony even moderately, such as a variation of sugars, or even the transference to a very different medium, such as potato, gelatin, etc. But with the fungi such changes would work most striking changes in morphology, and it is this sensitiveness on the part of pathogenic fungi to comparatively trivial variations in the medium that has made this study necessary. In essence, it is the higher degree of specialization of these fungi, compared to bacteria, that enables them to take on such different appearances—depending on the nutritional conditions which happen to be at hand.

LACK OF SATISFACTORY CLASSIFICATION

We believe that it is this inconstancy of morphology which has been the big stumbling block to a more general, certainly a more continued, study of the molds. But this is not all. A second obstacle consists in the fact that at present there are no satisfactory classifications of the

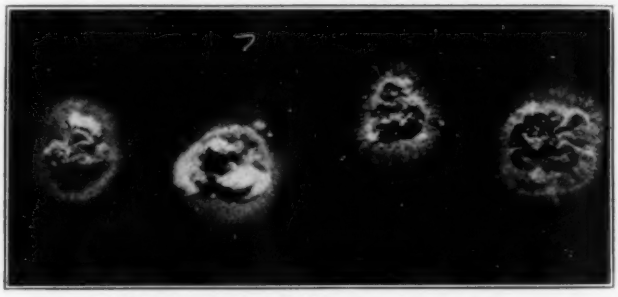

Fig. 3.—Culture Series 1. *Epidermophyton inguinale;* colony four weeks old. Tube 1, "all French" ingredients except the agar; Tube 2, "all French"; Tube 3, Mead's; Tube 4, Eflorose. No acid adjustment. Allowing for the "individual variation" of mold colonies, as far as appearance goes all four of these might have been planted on the same medium. Illustrates comparative adequacy of several maltoses for this species.

fungi from the systematic standpoint. Sabouraud's is a clinical one which depends on a foreknowledge of the source of the material, and only covers a limited number of species as compared to the whole broad general subject of mycology. What Sabouraud has done he has done well; but one has only to examine the list of names applied to genera (*Microsporon, Trichophyton, Epidermophyton, Achorion*) to recognize the futility of attempting to classify nonpathogenic fungi in relation to those from the systematic, botanical standpoint.

Castellani,[1] on the other hand, has given us a tentative working classification along these very lines, i. e., an arrangement into classes,

1. Castellani, A.: Milroy Lectures, J. Trop. M. **23**:101 (May 1) 1920; cont. **23**:117 (May 15) 1920; cont. **23**:133 (June 1) 1920.

orders, families, genera, etc., depending on the morphology of the organism. This is the rational classification, comparable and consistent with the classifications applied in biologic systems. The unfortunate feature of Castellani's classification is that he does not go far enough in that he fails to analyze Sabouraud's genera and to distribute the very differently appearing species under the proper genera. Examples are the achorions. The microscopic characters of *A. schönleinii* are very different from those of *A. gallinae* and *A. quinckeanum*. We might also cite *Trichophyton faviforme*. In short, what we need today is a revision of the classification of the fungi from the morphologic

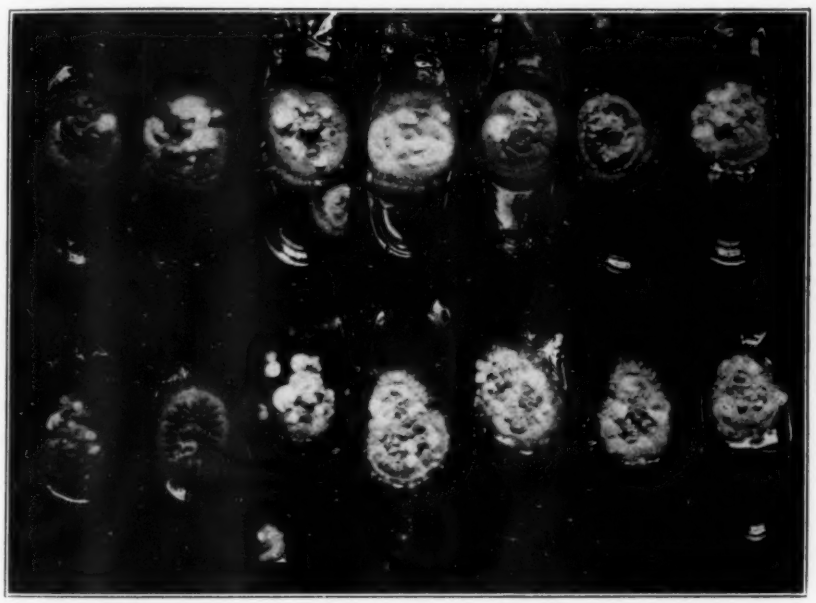

Fig. 4.—Culture Series 1. *Epidermophyton inguinale;* colony nine weeks old. Tubes 1 to 6 "all French" ingredients; Tube 7, "all French" except for Difco peptone. Bottom row: all American ingredients: first tube, Pfanstiehl maltose; second, Difco; third, Mellin's; fourth, Eflorose; fifth, Dolbey; sixth, Borcherdt's; seventh, Mead's. No acid adjustment. The Difco peptone and American maltose are a little remiss in not developing the peripheral fringe at this late date, but sufficient criteria still remain for certain identification. Illustrates comparative adequacy of several maltoses for this species.

(essentially microscopic) standpoint. With this at hand, supplemented preferably by an encyclopedic textbook, with full illustrations of type fructifications and other "organes," we should not experience a feeling of despair as we now do when we isolate an organism which does not compare with those illustrated in Sabouraud's or Castellani's books.

THE RESTRICTED FIELD OF MYCOLOGY

In the third place, mycology has a very restricted field. Its practical application lies in greatest part at present in the subject of ringworm: and, as this is not a matter of life and death ordinarily, there is not the zest to the subject that there is to that of bacteriology and animal parasitology. It is not as profitable a field as those, certainly not in proportion to the difficulties to be overcome.

We believe these factors are the three major lions in the way of progress in mycology. Of them the second, classification, cannot logically and seriously be attacked until the first, morphology, has been disposed of and made available for use in constructing a classification. The third will take care of itself, and the field broaden as it is cultivated.

Fig. 5. Culture Series 1. *Microsporon equinum*.. Colonies four weeks old. Tube 1, "all French" except the agar; Tube 2, "all French" except for Difco peptone; Tube 3, Difco maltose; Tube 4, Pfanstiehl; Tube 5, Mellin's. No acid adjustment. Striking contrast between the C. P. maltose (Tube 3) and the remaining four impure ones.

It would indeed be an achievement for such a subject as pulmonary sporotrichosis or systemic blastomycosis to be clarified by a dermatologist.

It is evident that all this is no one or two man task. We outline it rather to orient the general physician mycologically, and to explain the reason for our work here reported. This at present concerns the subject of culture mediums, a phase which is basic to, and indispensable for, any progress in mycology.

CULTURE MEDIUMS

The maltose ingredient has been every one's main concern so far. It is used in mediums today because the earliest workers began with it

and because Sabouraud insisted so strongly on its use for bringing out differential characteristics. Bodin,[2] for instance, used beerwort. Colcott Fox [3] and Sabouraud,[4] who followed him, used a solidified refinement of the same substance in the form of a very crude maltose. Fox and Blaxall's experience with mediums reads very much like what we shall say later, except that they ascribed the high acidity to the maltose rather than to the peptone. They, too, finally had to resort to imported French ingredients.

White [5] stood rather alone in finding that other maltoses (Lehn and Fink, and Grüblers) were equivalent to the crude French (Chanut).

The Maltose Situation in America.—As far as we can learn at present, few men have attempted the culture of ringworm fungi in America and at the same time seriously attempted to obtain the same morphologic characters that Sabouraud did. These men imported the French ingre-

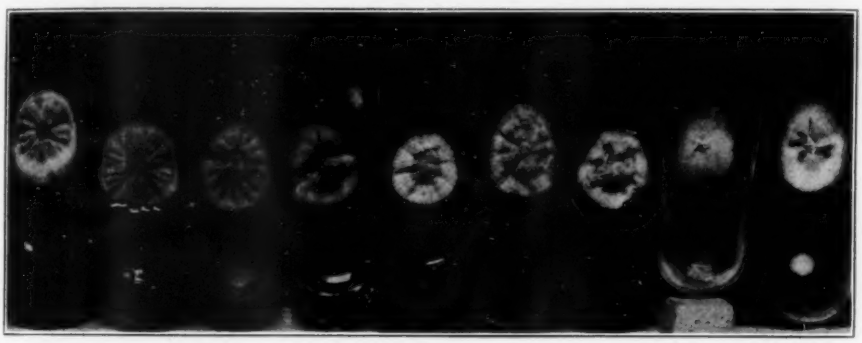

Fig. 6.—Culture Series 3. *Microsporon equinum*; colonies ten days old. Tubes 1 and 2, "all French" control. Remaining seven on American peptone, with acidity adjusted to + 1.8 with "hydrochloric acid albuminate." Maltose as follows: Tube 3, Mead's; Tube 4, Borcherdt's; tube 5, Mellin's; Tube 6, Pfanstiehl; Tube 7, Maltine; Tube 8, Difco; Tube 9, Dolbey. Obvious disagreements photographically with control except Tubes 3 and 6. The latter were too highly heaped up, and lacked the smaller secondary furrows. These differences increased as the colonies aged.

dients, and were therefore reasonably sure of comparable pictures. No doubt others, like ourselves, have attempted such work and obtained only passable results. Our experience is that some of Sabouraud's fungi give sufficiently characteristic growths for identification on mediums made from ordinary American trade ingredients. *E. inguinale* and *A. schönleinii* are examples, but others which do not grow typically

2. Bodin, E.: Les champignons parasites de l'homme, Paris, Masson et Cie, 1902, p. 107.

3. Fox, Colcott, and Blaxall: Brit. J. Dermat. 1896, pp. 242, 291, 337, 377.

4. Sabouraud: Les teignes, Paris, Masson et Cie, 1902.

5. White, C. J.: J. Cutan. Dis. **17**:1 (Jan.) 1899.

are the very important *M. audouini* and *M. lanosum;* and the gross appearance for these two is very important, because with several species closely related to them the microscopic appearance is identical, and gross appearances are therefore indispensable in order to distinguish them differentially. Compare *M. audouini* and *M. velveticum,* on the one hand, and the whole group of animal microsporons on the other.

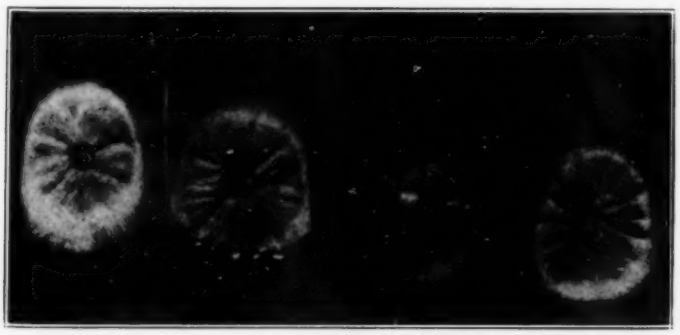

Fig. 7.—Culture Series 3. *Microsporon equinum;* colonies ten days old. Adjusted to + 1.8 with "hydrochloric acid albuminate." Tubes 1 and 2, "all French" control; Tube 3, "all French" except for Difco peptone; Tube 4, R. A. L. maltose. The third colony is moist, and the fourth not hairy enough as compared to the two controls.

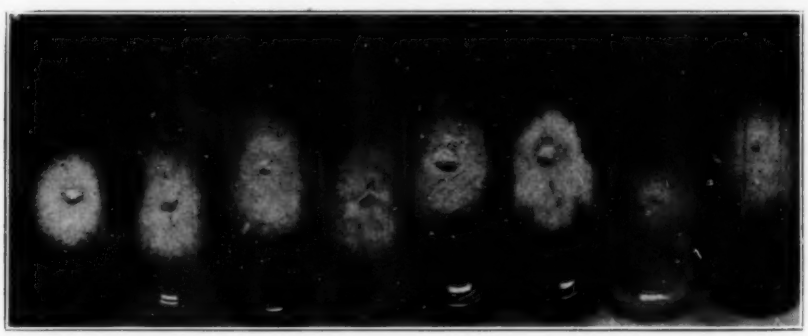

Fig. 8.—Culture Series 3. *Microsporon lanosum;* colonies ten days old. Tube 1, "all French" control. Remainder with Difco peptone, medium adjusted to + 1.8 with "hydrochloric acid albuminate" and containing American maltoses as follows: Tube 2, Mead's; Tube 3, Borcherdt's; Tube 4, Mellin's; Tube 5, Pfanstiehl; Tube 6, Maltine; Tube 7, Difco; Tube 8, Dolbey. The differences became more marked as the colonies grew older.

Now, the problem would be much simplified if a supply of all the French ingredients were at all times easily obtainable; but this is not the case. While we have been able to import all the other substances, we have not yet succeeded in obtaining any of the French crude

maltose. Others have had very much the same experience. Mr. Hodges, from whom we obtained our supply, had succeeded in getting some through a personal friend who was himself on the ground in Paris. And now that Sabouraud [6] writes us that there is no more crude maltose available, a fortunate departure has been precipitated from what was from the first an unsatisfactory medium for culture.

General Considerations of Sabouraud's Proof Medium.—This medium consists of:

Maltose (Chanut)	40 gm.
Peptone (Chassaing)	10 gm.
Agar	18 gm.
Water	1,000 c.c.

The maltose must be crude; the chemically pure will not do. Sabouraud's material is indeed crude, coming in fractured lumps about the color of sweet chocolate. The peptone is made by Chassaing, and we early found that it was the factor responsible for the rather high

Fig. 9.—Culture Series 3. *Microsporon equinum;* colonies ten days old; illustrating synthetic mixtures and inadequacy of dextrin combinations tried. Tubes 1 and 2, "all French" controls; Tube 3, dextrin 100 per cent. (of the whole sugar content) Difco maltose none; Tube 4, dextrin 90 per cent.—maltose 10 per cent.; Tube 5, dextrin 50 per cent—maltose 50 per cent.; Tube 6, dextrin 10 per cent.—maltose 90 per cent. The last colony was really not as good as it looks photographically. It was too highly heaped up in the center, and not coarsely hairy enough.

acidity of the French medium as compared with the American ($+1.8$ against $+1.2$). When one recalls how the composition of different peptones varies, and that the maltose is perforce crude, one must realize beforehand that an attempt to imitate them will be only a

6. Sabouraud writes, May 12, 1921, that "ne trouve plus en ce moment" and "nous ne pouvons plus nous procure de maltose Chanut." It appears that the history of the house of Chanut had been a checkered one. As far back as 1896 Colcott Fox and Blaxall (Footnote 3) stated that Sabouraud had told them that the factory was closed. In 1902 Bodin found that crude maltose was not procurable commercially (Footnote 2) "Ne se trouve plus dans le commerce." In spite of all this, small lots at least have within the last few years been filtering into America, and appear to be the genuine article.

hope for good fortune. Both are prepared by biologic methods, i. e., by the use of enzymes. Furthermore, the "impurities" in maltose consist not alone of such carbohydrates as dextrin and glucose, resulting from the incomplete enzymic action, but also certain nitrogenous substances. All of these will vary with the method of preparation of the specimen of crude maltose and are in themselves important substances in the nutrition of the fungus which is to be cultured. Therefore, the combination of these variables—peptone, maltose, impurities—appears

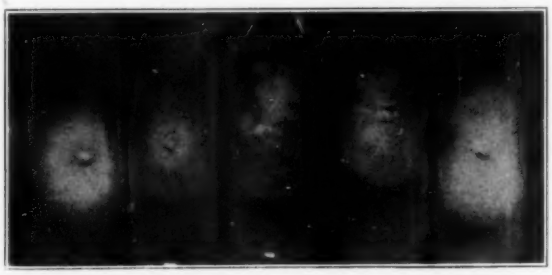

Fig. 10.—Culture Series 3. *Microsporon lanosum;* colonies ten days old. Same test and ingredients as in Figure 9, except that only one control is shown at the left. In both Figures 9 and 10 the last tubes show that it is the maltose that is almost "saving the dextrin's face," but falling short.

Fig. 11.—Culture Series 3. *Microsporon equinum*; colonies ten days old. Tubes 1 and 2, "all French" controls. Remaining four contain varying proportions of glucose and maltose; Tube 3, glucose 100 per cent. (of the whole carbohydrate content)—maltose none; tube 4, glucose 90 per cent.—Difco maltose 10 per cent.; Tube 5, glucose 50 per cent.—maltose 50 per cent.; Tube 6, glucose 10 per cent.—maltose 90 per cent. Whereas in the illustration all of the latter four appear very similar, yet there are characters (color, moistness, etc.) not brought out photographically which make the last combination the one of choice.

insurmountable. However, the final determination could only be made by trial.

AUTHORS' STUDIES

We have conducted four series of tests. In all, the tubes were run in duplicate, i. e., sowings were made on two tubes instead of one of

each of the many combinations. This was done to guard against interruption of the series by the occasional contaminations, the occasional unexplainable failure to "take," and the certain degree of individual variation that always obtains in ringworm colonies. Purity of our culture has always been kept in mind and controlled from time to time. In each series, a control was run on mediums made from imported "all French" ingredients, and the growth which developed on this (in duplicate as in all other tubes) was used as a standard. The general plan was to make various combinations of reactions and ingredients in mediums to see whether the growths developing on them would tally with the "all French." We have used nine different organisms, compounded about 300 combinations of maltoses, acidities,

TABLE 1.—VARIOUS BRANDS OF MALTOSE USED IN THE AUTHORS' TESTS *

	Maltose by Benedict	Barfoed†	Moisture	Achroo-dextrin
Difco Stiehl	100	Negative	....	0.0%
Pfanstehl	83	Strong	2.3%	14.7%
Dolbey	72	Strong	7.0%	21.0%
Borcherdt	81	Moderate	2.5%	16.5%
Mead	55	Moderate	5.1%	39.9%
Mellin's	55	Weak	5.5%	39.5%
Maltine	66	Strong	30.0%	4.0%
Du Sabouraud ⁋	104‡	Strong	10.7%	? §
R. A. L. ¶	65	Very Weak	19.0%	16.0%

* Approximate estimation by Dr. R. L. Stehle. Accurate figures are unobtainable for mixtures of carbohydrates on account of limitations of present chemical methods.

* There was no starch in any of the brands.

* Eflorose, a confectioners' syrup, used only in the first series of tests, was not analyzed.

† A positive Barfoed test represents the presence of dextrose. The maltose percentages therefore include dextrose, and the actual quantity of sugar present is smaller than indicated by the percentages, since the reducing power of dextrose exceis that of maltose. The dextrin percentages are consequently somewhat higher than the figures given.

‡ This high figure is due to (1) the reducing "figure" of maltose being so low (as compared to glucose), and (2) the fact that glucose is so largely present in the mixture.

§ This figure not obtainable on account of the high figure for maltose. The dextrose figure is the difference between the maltose and moisture.

⁋ Imported French. Furnished through the kindness of Mr. Robert L. Hodges, University of Alabama, and presumably the product of Chanut.

¶ Substitute crude maltose proposed by a French manufacturer.

peptones, etc., and as such were run in duplicate it has meant, counting the controls, that upward of 700 tubes have been studied in all.

Several of the specimens of maltose used (Table 1) will be recognized as proprietary infants' foods. As far as we could ascertain, only one chemically pure maltose is made in America (Difco).

Series 1.—In this series seven different known organisms were used as indicators, four of which were sent to us by Prof. Sabouraud and the remainder isolated in our laboratory. The following organisms were used: *M. lanosum, M. equinum, E. inguinale, T. effractum, T. plicatile, T. radiolatum* and *T. gypseum* (Sabouraud).

We used ten different American sugars, filtered through both cotton and French and American filter papers, and with French and American agar. The stoppers of some tubes were paraffined or covered with lead foil to exclude air, and others were not. All tubes were kept in

semidarkness at room temperature. We found that the method of filtering had no effect on the cultures, that the same appearance obtained on American as on French agar, and that paraffining had no effect on the growth characteristics until after the lapse of the several weeks during which observations are of use in identifying these cultures. After that time the medium dried out naturally more rapidly than did the tubes stoppered with paraffin.

Other factors, however, did make a difference. As to the effects induced by American sugars, *T. effractum, T. plicatile, T. radiolatum* and *T. gypseum,* showed the same features as on "all French" mediums. *E. inguinale* showed changes of one or another sort but never so extreme but that enough characteristics remained to permit fairly ready and certain identification. With *M. lanosum* and *M. equinum,* the American sugars produced very marked variations, and these must be considered useless for purposes of universal identification.

Fig. 12.—Culture Series 3. *Microsporon lanosum;* colonies ten days old. Same test as Figure 11, except that only one control is shown at the left. Again the 10-90 combination of glucose and maltose (last tube) gives the closest approach to the control.

A few tests of American against French peptone were made on otherwise "all French" mediums, and notable and consistent differences noted with the two microspora, all in favor of the French peptone. As stated before, with the other five organisms the American was as useful as the French peptone.

The effect of this series, in respect to all seven organisms, was to show: (1) that we could use American agar, (2) that stoppers may be paraffined without detriment, (3) that the method of filtering was unimportant, (4) that the matter of peptone and maltose was unimportant with some of the fungi (the four trichophytons that we tested and *E. inguinale*), and (5) that *M. lanosum* and *M. equinum* were sensitive to all the different sugars and to peptone. This series had the effect of narrowing our further examinations to these two organisms

and of requiring for the present the use of French peptone with these. It is obvious that a synthetic American medium, to be of general value, must bring out the characteristics of every species, not simply the majority or any number short of 100 per cent.

Series 2.—This series, therefore, was carried out with only these two microsporons and on all the sugars used in Series 1. We have remarked before that we found the higher acidity of French medium was referable to the peptone in it, and we therefore tried to cover this point. We ran a series with (1) French peptone and (2) American peptone adjusted up to the French acidity with hydrochloric acid. The attempt was a failure because most of the adjusted tubes would not support growth; the organism could not stand it, and the occasional cultures which did develop did not compare at all with the "all French" control. Neither did any of the American sugars (we had tried only three in this respect in Series 1) when combined with French peptone agree

Fig. 13.—Culture Series 3. *Microsporon lanosum;* colonies seventeen days old, a little older than in Figure 8; corrected to + 1.8 with "hydrochloric acid albuminate" (in tubes where Difco peptone was used). Tube 1, "all French" control; Tube 2, "all French" R. A. L. maltose; Tube 3, "all French" except for American peptone; Tube 4, 50 per cent. dextrin—50 per cent. maltose; tube 5, 50 per cent. glucose—50 per cent. maltose; Tube 6, maltine; Tube 7, Difco. Tubes 1 and 5 are the most perfect agreements of all our five or six hundred trials. All the others in this picture have developed insufficient duvet—are too flat.

with the "all French." The effect of this series was (1) to indicate that free hydrochloric acid cannot be used as an adjuster, and (2) to confirm the impression that French peptone was essential.

Series 3.—In this series we proceeded along three lines. First, we adjusted acidity as in Series 2, but used an "acid albuminate" instead of free hydrochloric acid for adjusting. The acid albuminate was made by previously boiling decinormal hydrochloric acid with agar. The results were that, whereas this time growth took place freely enough on such adjustments, they did not compare in characteristics with colonies on French peptone or with the standard.

The second line in Series 2 was a rough preliminary test of synthetic mixtures of the probable ingredients of Sabouraud's maltose, i. e., dextrin, glucose and maltose, all chemically pure and American. French peptone was used with these. The combinations tried were: dextrin 100 per cent.; dextrin 90 per cent.—glucose 10 per cent.; dextrin 50 per cent.—glucose 50 per cent.; dextrin 10 per cent.—glucose 90 per cent.

Glucose 100 per cent.; glucose 90 per cent.—maltose 10 per cent.; glucose 50 per cent.—maltose 50 per cent.; glucose 10 per cent.—maltose 90 per cent.

Maltose 100 per cent.; maltose 90 per cent.—glucose 10 per cent.; maltose 50 per cent.—glucose 50 per cent.; maltose 10 per cent.—glucose 90 per cent.

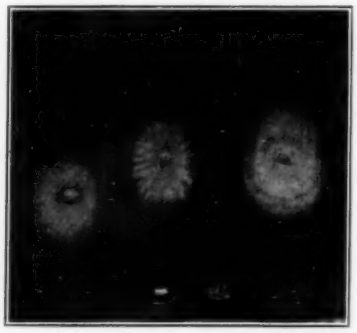

Fig. 14.—Culture Series 3. *Microsporon lanosum;* colonies ten days old. Tube 1, "all French" control; Tube 2, "all French," except for Difco peptone (adjusted to + 1.8); Tube 3, "all French," R. A. L. maltose.

Results.—The nearest approach to the "all French" occurred in those tubes in which there was at least a notable quantity of glucose. One of the best reproductions occurred in the glucose 90 per cent.—maltose 10 per cent. combination.

Along the third line, we checked up and confirmed previous findings as to the effect of American and French peptone and agars.

The effect of this series was to indicate that acid adjustment alone would not bring the American peptone up to the French, and that therefore work would have to be further developed along this peptone line as well as along the maltose line. It also pointed to glucose as an essential carbohydrate in addition to the maltose, and appeared to exclude dextrin.

Series 4.—It then occurred to us that possibly the differing effects of American and French peptones were referable to a differing concentration of certain essentials, and that the American could be made to

approach the French by varying the quantity. Accordingly, graded concentrations of both French and American peptone were used, extending from 0.5 per cent. to 3 per cent.

Along the carbohydrate line, on the other hand, it was brought out in Series 3 that glucose induced a growth of mycelium particularly, resulting, as we desired, in a more hairy appearance than when maltose alone was used. This was particularly marked with *M. lanosum*. It was decided, therefore, to ascertain what effect the three carbohydrates (dextrin, glucose and maltose) would have in the absence of complicating peptone in bringing out the different units—the A. B. C's—which go to make up the characteristics of a culture. By units we mean such things as luxuriance, powderiness, moistness, hairiness, color, etc. Therefore the two microsporons were planted on American chemically pure glucose, dextrin and maltose, in the strength of 40 gm. of each,

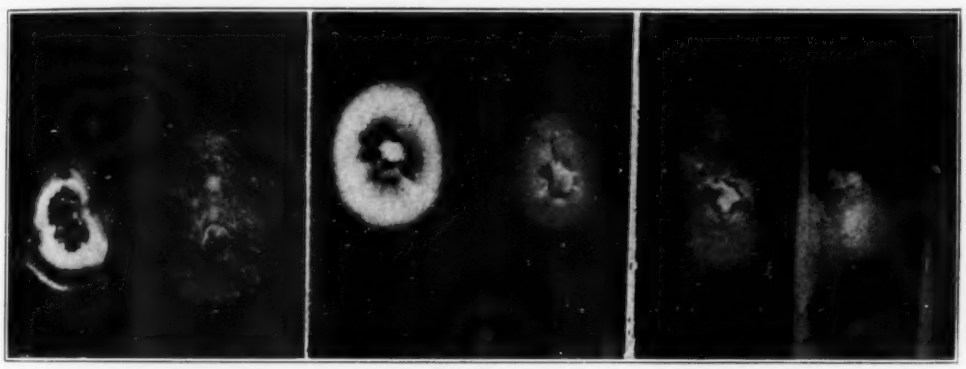

Fig. 15.—Culture Series 4. *Microsporon equinum;* colonies fourteen days old; grown on graded concentrations of French and American peptone alone—no carbohydrates of any sort. Tubes 1 and 2 contain 3 per cent. peptone, French at the left, American at the right; Tubes 3 and 4, 1 per cent., French at the left, American at the right; Tubes 5 and 6, peptone, 0.5 per cent., French at the left, American at the right. The proper wooliness was not elicited by any American concentrations tried, and not in weaker French concentrations (0.5 per cent.).

separately, per 1,000 cubic centimeters. The results were most striking. In the case of the peptone cultures, hairiness developed only in the 2 per cent. and 3 per cent. French peptone mediums. All the others were moist, even the 3 per cent. American peptone. The bulk of growth was quite satisfactory on the 3 per cent. American peptone.[7]

The growths on the three sugars showed no hairiness whatsoever. It was only possible to see the colony by slanting the tube in the most advantageous light, and then the surface growth was discovered to

7. In all American tubes the organism extended deeply into the medium. This was particularly the case with the weaker concentrations.

consist of translucent filaments which crept closely over the surface. That is, the sugars were conducive to a flat, translucent, moist type of colony.

The general effect of both these tests was to show that the course of studies toward eliciting wooliness lay in some other direction than the sugars and the American peptone. In this connection we have noted for a long time that the French peptone appears much cruder than the American. It has a distinct yellow color and comes in coarse granules. No doubt there are nitrogenous or other impurities intermixed in it which are responsible for the wooly appearance. These are the sub-

Fig. 16.—Culture Series 4. *Microsporon lanosum;* colonies fourteen days old; on chemically pure carbohydrates only (4 per cent.)—no peptone. Tube 1, French maltose; Tube 2, French glucose (masse); Tube 3, American glucose (Mulford); Tube 4, American dextrin (Merck); Tube 5, Difco maltose. There are scanty surface growths on all tubes, but they are moist and translucent, and do not photograph well. The darker color of tube 4 is due to its red color.

stances which should be logically intermixed (amino-acids such as tryptophan, and possibly urea, phosphates, ammonia salts, etc.) in any further attempts at synthesizing an American medium comparable to Sabouraud's proof medium, a ponderous and unpromising prospect indeed. Certainly we have been obsessed by the maltose factor of the proposition and have been neglecting the nitrogenous and inorganic salt phases.

Just as we were completing the last set of tests we received word from Sabouraud that the original crude maltose was no longer obtainable and that glucose agar was as useful as maltose agar. This was

a surprise, in view of the impression we have gained from Sabouraud's book; and clearly this course has been forced on French mycologists as a result of French conditions.

CONCLUSIONS

1. Only certain species of molds (probably a very small number indeed) require crude French maltose and French peptone for identification. With many, American chemically pure (Difco) products serve perfectly well and no adjustment of reaction is necessary.

In respect to the "maltose-sensitive" organisms:

2. In the present state of the French maltose market and the absence of substitutes, we shall have to depend on glucose agar.

3. Imported French peptone (Chassaing) must be used.

4. American agar may be used, and either American cotton or filter paper used for filtering.

5. No adjustment of reaction is necessary as this is taken care of by the French peptone.

6. There is no American maltose, either chemically pure or crude, that can be substituted for the original article. The recently recommended R. A. L. imported French sugar will not serve. This has been confirmed by Sabouraud in a personal communication.

7. American peptone (Difco) must not be used.

SIGNIFICANCE OF RESULTS

What does all this mean in relation to the general broad proposition of ringworm culture? We refer to methods which always have been uncertain and unsatisfactory, and are now even more so, with the present lack of French maltose. We have intimated before how variable the composition of the original "proof" medium was, composed as it was of biologic ingredients whose composition may vary from time to time. Even if the original French maltose should again become available, we should be no better off, for there is no guarantee that it would be the same 100 years from now. The same is true of the French peptone. Methods of manufacture could change during that time, firms go out of business, etc.

It means, then, this: The consummation devoutly to be wished is a new medium composed of definite, chemically pure ingredients, of reasonable cost, adjusted to a standard acid figure, which will approach as closely as possible Sabouraud's pictures. Something of this sort is quite necessary as a permanent foundation for the study of such pleomorphic, protean organisms as these molds.

This is an exacting and radical proposition, but such surgery often proves to be best in the long run. It would undoubtedly involve the abandonment of Sabouraud's maltose characteristics—really, they are

done for now—and doubtless some modification of the glucose figures of some of the molds. It would not mean that the whole of the gross morphologic chapter would have to be rewritten, and of course it would not involve the clinical, statistical or microscopic sections of his book.

Anything short of a new culture medium would be only perpetuating the unsatisfactoriness of the original "proof" medium. As seen at present, chemically pure glucose promises best and will doubtless be perfectly satisfactory on the carbohydrate side. A modified Raulin's fluid should be kept in mind from the nitrogenous side, etc., and may some day prove useful in place of peptone, somewhat as follows:

Tartaric acid	4 gm.
Ammonium nitrate	4 gm.
Ammonium phosphate	0.60 gm.
Potassium carbonate	0.60 gm.
Magnesium carbonate	0.40 gm.
Ammonium sulphate	0.25 gm.
Zinc sulphate	0.07 gm.
Iron sulphate	0.07 gm.
Potassium silicate	0.07 gm.
Water	1,500 c.c.

This was originally recommended for growing *Aspergillus niger*. Work along this line remains to be done.

As the ringworm culture problem stands today, we recommend that Sabouraud's maltose characters be abandoned and that the work be pursued on glucose mediums made from American ingredients, with the exception of the peptone. This must be French (Chassaing).

TABLE 2.—INDEX OF INFORMATION BROUGHT OUT BY THE ILLUSTRATIONS

1. Adequacy of certain American maltoses for "maltose-insensitive" species. Figures 1 (in part—[Pfanstiehl and Mellin's]), 2, 3 and 4.
2. Inadequacy of American maltoses for "maltose-sensitive" species. Without acid adjustment, Figures 1 (in part) and 5. Also with acid adjustment, Figures 6, 8 and 13.
3. Necessity for French peptone. With no acid adjustment, Figures 1, 4 and 5. Even with acid adjustment, Figures 13 and 14. (At least desirable if not "necessary" in the case of Figure 4.)
4. Uselessness of proposed French maltose substitute R. A. L. Figures 7 and 14.
5. Effect on morphology of graded amounts of peptone, both American and French — no carbohydrate. Figure 15.
6. Effect on morphology of carbohydrates alone — no peptone. Figure 16.
7. Suitableness of American agar. Figures 1 and 3.
8. Non-importance of filtering methods. In Figures 1 and 4, Tube 1 was filtered through French filter paper, Tube 3 through American filter paper, and Tube 4 through cotton.
9. Nonimportance of paraffining stoppers. In both Figures 1 and 4, Tubes 1 and 3 were paraffined, while Tubes 4 and 5 were not.

POROKERATOSIS

REPORT OF A CASE *

CARROLL S. WRIGHT, M.D.
Instructor in Dermatology and Syphilology, University of Michigan Medical School
ANN ARBOR, MICH.

In 1893 Mibelli [1] and Respighi [2] simultaneously called attention to a form of dermatosis not previously described. To this condition Mibelli gave the name of "porokeratosis," while Respighi termed it "hyperkeratosis eccentrica." During the twenty-seven years that have intervened since the first description of this affection, not over sixty cases have been reported in the literature. In this country in particular the condition is extremely rare, cases having been published only by Hutchins, Gilchrist, Wende and Heidingsfeld. Since 1898 no authentic case of porokeratosis occurring in the United States has been reported, Heidingsfeld's in 1905 only simulating the condition histologically. The following case was seen recently in this hospital.

REPORT OF CASE

History.—The patient, a Greek, 40 years old, entered the dermatological service of the University Hospital because of lesions on the hands, buttocks, legs and feet. He described lesions corresponding exactly to those he presented as occurring on the hands and feet of his father, and said that the father told him that the grandmother had had the same condition. The father told him also that it was a family disease occurring throughout the life of those affected, all efforts toward a cure being useless. Although the patient said that his wife and four of his children were entirely free from lesions of any kind, a fifth child, a girl 9 years old, had warty appearing elevations on one leg. The patient gave an indefinite history of having had a soft, painful, penile lesion at the age of 15. This was accompanied by an eruption over his body, the details of which he had forgotten.

The lesions which he presented had been present since infancy. The exact date of their appearance he does not know, but was told by his father that his feet were first affected, when he was but 1 or 2 years old. Later, new lesions appeared on the scrotum, buttocks and penis, and finally on the hands and present sites of election. He described them as appearing first as small brownish

---

* Read before the Section on Dermatology and Syphilology at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

1. Mibelli: Contributo allo studio della ipercheratosi dei canali sudoriferi, Gior. Ital. d. mal. ven. 1893, p. 313; Beitrag zum Studium der Hyperkeratosen der Knaueldrusen ganges, Monatsch. f. prakt. Dermat. **17**:417, 1893, translation of (1).

2. Respighi: Di una ipercheratosi non ancora descritta, Gior. ital. d. mal. ven. 1893, p. 356; Ueber eine noch nicht beschreibene Hyperkeratose, Monatsh. f. prakt. Dermat. **18**:70, 1894.

spots which, increasing in size, became depressed in the center. They were accompanied by a severe pruritus. It was this subjective symptom that brought the patient to the hospital.

Examination.—The patient was a well nourished man of fair appearance. His scalp was clean. The pupils were equal and reacted to light and accommodation. There was slight axillary and inguinal adenitis; the spleen and liver were not palpable, and the heart and lungs were normal. The reflexes were present and equal. The blood Wassermann reaction was negative.

Back of the left ear, on the forehead, neck, hands, buttocks, scrotum, feet and legs were about twenty raised, verrucous lesions. These varied in size from those a few millimeters in diameter to some as large as a dollar. For the most part they were noninflammatory, but on the scrotum and in the peri-anal region they were mildly inflamed and slightly eroded. The smallest lesions were barely visible and presented themselves as brownish, slightly elevated papules. These were found chiefly on the forehead and back of the ear. Lesions about a centimeter or more in size presented a distinctly verrucous appearance, and in the instances of the older ones showed a raised, wavy border and a depressed center. Lesions of this type were entirely confined to the feet. Examination of the border of the lesion revealed a shallow groove running around the summit, this groove being slightly overlapped by a flap of its internal wall. The height of this border varied from 1 mm. to 5 or 6 mm. The depressed center presented itself as a smooth, callous surface, showing entire absence of hair follicles and having a brownish pigmentation. There were definite scratch marks over some of the lesions. The palms and soles were free and the nails were not affected.

Microscopic Examination.—In order to make a complete pathologic examination of this condition, it was thought necessary to study lesions in various stages. For this purpose, five lesions were excised, varying from the smallest demonstrable papule to the larger, ringed patches. The tissues were fixed in formol and in alcohol, imbedded and cut in paraffin. In making the stains hematoxylin and eosin, toluidin blue, Unna's polychrome methylene blue, neutral orcein and Pappenheim's stain were employed.

The first sections studied were cut from a lesion about 2 mm. in diameter, excised from the forehead. A portion of the surrounding skin was taken for comparison. The process at this stage showed an acanthosis, accompanied by a slight degree of hyperkeratosis. The horny layer for the most part was composed of cells with indefinite outlines and well-stained, shrunken nuclei. There was considerable scale formation. The entire thickness of the stratum corneum was slightly less than that of the underlying stratum granulosum, which was composed of from three to four layers of cells. The stratum lucidum was wholly undemonstrable. The hair follicles were distended and filled with horny material which stained deeply with eosin. Other horny plugs could be traced through serial sections to the sweat ducts, but these were by no means prominent. The acanthosis resulted from a thickening of the prickle cell layer. This layer showed in its central portion many distended and separated cells. The basal columnar layer of cells was unchanged. One of the most striking features of the early stage was the marked prolongation of the interpapillary tufts deep into the cutis. The cutis also shared considerably in the changes. The capillaries show dilatation and were surrounded by collections of lymphoid cells. The infiltration of these cells was most marked in the center of the lesions, large collections being found around the hair follicles. There were only few sweat gland ducts visible in the corium.

The second piece of tissue studied was a slightly larger lesion than the first. It showed no increase in the acanthosis, but a distinct increase in the hyperkeratosis over the earlier lesions. The stratum corneum here was made up of from ten to twenty layers of cells, being thickest in the region of the follicles and orifices of the sweat glands. The cells had fairly definite outlines and well stained shrunken nuclei as in the first section. Projecting down into the distended openings of the follicles and sweat ducts were definite conical plugs made up of cells, some of which were entirely cornified, while others showed definite nuclei. The marginal cells of these plugs mingled with those of the hyperkeratotic stratum corneum. Throughout the stratum corneum there were inclusions of hyaline pink-staining material and numerous minute abscesses. The stratum granulosum was thinned out except in the region of the follicles, where it was composed of from three to four layers of cells. The stratum lucidum was again invisible. The cutis showed capillary and lymph space dilatation and considerable round cell infiltration. Here again there was no demonstrable change in the ducts of the sweat glands, but there were few of these in the section. Unfortunately, this bit of tissue was not excised deeply enough and extended but a little distance below the papillary layer of the corium.

The third section was taken from the leg and was the largest section, showing no central depression. The hyperkeratosis here was equal to the acanthosis. It was more compact, and no cell outlines or nuclei were to be seen. The same was true of the hyperkeratosis in the follicular openings. The plugs were very compact and penetrated deeply into the follicles. The stratum lucidum was thickened and distinctly visible. The stratum granulosum in places consisted of from six to eight layers of cells. In the corium there was more marked dilatation of the lymph spaces and capillaries than in the previous sections and a marked edema. In some places the walls of the blood vessels showed endothelial proliferation. There was also some dilatation of the sweat ducts. The picture was much the same as that of a verruca.

The fourth and fifth pieces of tissue were taken from lesions which macroscopically showed the raised peripheral wall with its characteristic crater and depressed center. The wall in the first of these lesions was only slightly elevated, while in the second it was about 5 mm. in height. The central area showed a much thinned out epidermis, and the hyperkeratosis was much less marked, although very compact. There was a total absence of hair follicles and sebaceous glands in this depressed center, but an occasional sweat duct was visible. The peripheral wall was formed by the markedly thickened stratum corneum and the hyperacanthosis of the prickle cell layer. Over the seam of the wall the hyperkeratotic tissue showed many well stained, atrophic nuclei. At no other places in the stratum corneum were they visible. By studying serial sections, numerous sweat ducts could be seen to converge toward the seam of the peripheral wall. These ducts were somewhat dilated, and the horny plugs reached down into their orifices. The cutis showed an increase in the collagen. The cellular infiltration was most marked beneath the wall.

REVIEW OF THE LITERATURE

In 1887, Domenico Majocchi observed a case of the affection in a 15-year old boy. He did not recognize its nature and presented it to his pupils at the University of Parma as a case of ichthyosis hystrix. At that time a photograph was made of the lesions on the forearm of

the patient and presented to the Institute of Dermatology at Parma. Six years later the same boy was seen by Mibelli,[1] who recognized the lesions as exceptional and different from the condition previously recorded. This case with two others he reported in the Italian literature, giving a full description of clinical and histologic findings, together with a résumé of previously described entities with which the condition could be compared. The picture, as Mibelli presented it, consisted of lesions beginning as warty, dry, cone-shaped elevations less than 1 cm. in diameter, which spread peripherally, leaving a depressed, dry, callous center. The border took on special characteristics unlike those of any other disease. Mibelli described it as having the appearance of a dyke

Fig. 1.—Typical lesions of porokeratosis, showing peripheral wall and central depression.

with a shallow central depression at its summit. In one instance a lesion reached such a size that the entire forearm and hand were covered. There was a predilection for the hands, face, genitals, legs and feet. Mibelli designated the disease as an essentially chronic one, beginning in the earliest years and continuing throughout the life of the patient. Attention was called by him to the hereditary tendency of the condition. As an example, he mentioned that two of his cases occurred in brother and sister.

In making a histologic study, the youngest lesion excised was two years old. Mibelli stated that the disease began as an acanthosis of the

surface epithelium, accompanied by a hyperkeratosis. In an advanced stage the hyperkeratosis stopped and there was an atrophy of the prickle cell layer through pressure of the already formed keratoma. In these places the hair follicles and sebaceous glands were absent. The process affected chiefly the sweat gland pores, which were filled with a horny black layer. The center of the duct projected out like a plume. It was by a coalescence of a number of these plugs that the ridge was formed which distinguished the advancing border of the affection. In the cutis there was a dilatation of the vessels of the papillary and sub-papillary parts. About the walls of the vessels there was an infiltration of lymphoid cells. In no place was there migration of these cells into the interspinous spaces of the prickle cell layer. The most important changes Mibelli believed to be in the coil of the sweat gland and its outlet. Where the interepidermal part of the duct was still patent, for the most part, notwithstanding keratinization, the coil still retained its normal dimensions but was deformed by localized dilatations which in some instances looked like cystic enlargements. Its epithelium was much reduced and compressed. In later stages new collagenous tissue appeared between the loops of the coils and gradually led to atrophy. The rest of the cutaneous tissue also atrophied, leading to central depression.

Respighi's [2] simultaneous article in the same journal contained a report of seven cases. He termed the affection "hyperkeratosis eccentrica" and divided the lesions into five distinct forms: (1) miliary to (2) lentil to (3) guttate-sized papules, (4) ringed lesions with a wall and a central clear space, and (5) cone or shell-shaped papules found only on the tips of the toes. He found that the nails were secondarily affected and described them as cloudy, brittle and falling off easily. Spots were found on the palms and soles.

The histology in these cases followed closely that of Mibelli, but more stress was laid on the involvement of the follicles with horny plugs which penetrated almost to the acini. Respighi found that the marginal wall was formed by the hyperkeratosis combined with thickened papillae. It was his idea that there was a parasitic hyperkeratosis or parakeratosis of the mouths of the tubular and acinous glands.

In the following year an attempt was made by Tommasoli [3] to prevent the recognition of porokeratosis as a distinct type of dermatologic affection. Without personally observing the cases, he maintained that the term porokeratosis was quite superfluous, as there were several forms of keratodermatitis attended by marked keratotic changes in the

3. Tommasoli: Sulla nuova ipercheratosi recentemente studiata dal Professor Mibelli e dal Dott. Respighi, Comment clin. d. mal. cut. e gen. ur., 1894, No. 1.

Fig. 2.—Typical late lesion, showing crater at the summit of the peripheral wall.

glandular follicles, particularly of the sweat glands, which, even if less marked than in porokeratosis, could be attributed to their relatively shorter duration. He placed the affection under the classification of the pseudolichens and suggested the name of "circinate pseudolichen porokeratosis." It was Tommasoli's idea that there was an autotoxic etiology for the condition.

In response to this article, Mibelli [4] published a lengthy refutation in which he insisted that the clinical and histologic characteristics of the disease described simultaneously by himself and Respighi were entirely different from any other condition. He states that the presence of keratosis in the gland ducts in other conditions, such as Darier's disease, pityriasis pilaris and lichen planus, was merely an associated finding and not the preponderating cause.

Respighi,[5] in 1895, having seen his eighth case, published a new work in which he discussed his attempts to prove that there was a

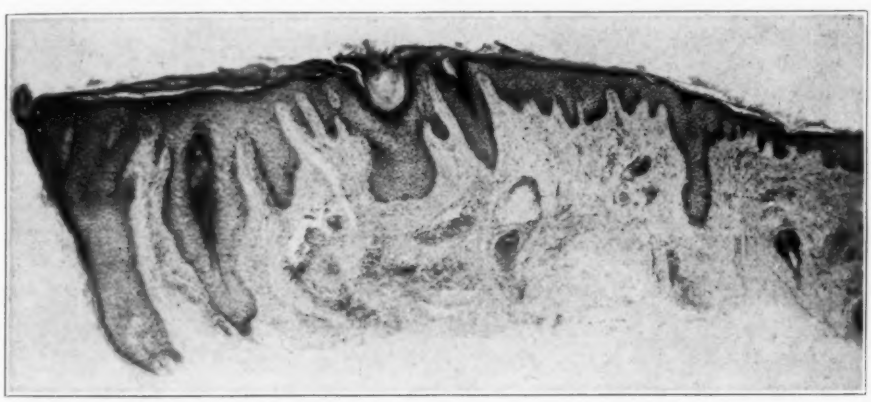

Fig. 3.—Biopsy of smallest demonstrable lesion, showing hyperkeratosis, plug in hair follicle, acanthosis, thickening and dipping down of interpapillary tufts and inflammatory reaction in the corium.

parasitic cause, and his negative results. In this article he stated that he refused to accept the hypothesis of Mibelli that the condition results from an alteration of the sweat apparatus, and held that Tommasoli's suggestion of its being an autotoxic keratodermatitis was untenable. The fairly definite family history would preclude the latter theory.

---

4. Mibelli: Sulla porokeratosi: a proposita di una critica. Gior. ital. d. mal. ven. 1894; Ueber die Porokeratose. Monatsh. f. prakt. Dermat. **20**:309, translation of (6).

5. Respighi: Sulla iperccheratosi eccentrica, Gior. ital. d. mal. ven. **1**:69, 1895; Brit. J. Dermat. **7**:1895; Ueber die Hyperkeratosis Excentrica: Monatsh. f. prakt. Dermat. **21**:499, 1895, translation of (8).

In response to this second article of Respighi's, Mibelli [6] insisted on the interpretation he had before given, and the title of "porokeratosis." At the meeting of the Italian Society of Dermatology and Syphilology in October, 1895, the question was discussed pro and con by the two men; Respighi [7] at that time presented three new cases, showing photographs and histologic preparations. At this meeting Majocchi expressed his opinion that the disease was a hyperkeratosis of the gland pores, but he considered it a variety of ichthyosis in which hyperkeratosis of the gland ducts predominated.

Fig. 4.—Biopsy of larger verrucous lesion. Marked hyperkeratosis, plug in follicle and acanthosis.

Later, in a report presented to the International Congress on Dermatology in London (Aug. 1, 1896), Mibelli [8] stated that the kera-

---

Mibelli: Iperkeratosi Eccentrica. Duex mots de response au Dr. Respighi, Gior. ital. d. mal. ven. **2**: 1895.

7. Respighi: Di una singolare ipercheratosi, Gior. ital. d. mal. ven. **2**: 1896, (communication to the annual reunion of the Italian Society of Derm. and Syph., held at Rome in October, 1895).

8. Mibelli: L'etiologia e le varieta delle cheratosi, Gior. ital. d. mal. ven. **4** and **5**: 1896.

totic cone was never seen in a follicular orifice, but always in a sweat gland orifice, and that the hyperkeratosis occurring in a follicular orifice did not resemble in color, form, structure or development that found in a sweat pore.

About this time the first case was reported in America by Hutchins.[9] In his patient the disease began at the age of 2 on the palms and spread peripherally. The family history was negative. Clinically the condition corresponded to Mibelli's description, except for the subjective symptom of itching. Unfortunately, Hutchins was unable to

Fig. 5.—Cross-section of plug deep in epidermis, inflammatory reaction in papillary and subpapillary layers of cutis.

obtain any sections for histologic study. Because of the involvement of all of the epithelial structures, he suggested the name of "panokeratosis or poropanokeratosis." To him goes the credit for reporting the first case seen in this country, although Stelwagon in his treatise on dermatology tells of a case seen by him in 1887, the true nature of which he did not recognize until some years later.

9. Hutchins: A Case of Porokeratosis Mibelli, J. Cutan. Dis. **14:** 1896.

At this point it would be most logical to mention the later American reports. The second report to be published in this country was that of Gilchrist [10] in 1897. His patient, a man 21 years old, had had the disease since the age of 5. In the same family Gilchrist traced eleven cases of the affection, thus giving ample proof of the hereditary tendency. In experiments with various forms of treatment he obtained good results with excision and with actual cautery, but found that recurrence took place following curettement and application of silver nitrate.

Wende,[11] in 1898, saw a single lesion in a woman, aged 45 years. It had begun at the age of 45 as a small, rough, scaly plaque between the thumb and finger of the left hand. After a year of quiescence it began to spread peripherally and became depressed in the center. It was accompanied by a severe pruritus. Histologically, he found the stratum lucidum to be barely visible, but the stratum granulosum was hypertrophied, especially near the sweat ducts. Thirty attempts at inoculation were unsuccessful with the exception of one instance in the original patient in which a lesion appeared accompanied by marked itching and histologically corresponding to porokeratosis. The patient, fearing the development of a second patch like the original, insisted on early excision of the experimental lesion.

Heidingsfeld,[12] in 1905, reported a case in the American literature of a man, aged 26, who for eight years had had an eruption of the left leg, the affected area presenting a pinkish-white color, somewhat sclerotic and studded irregularly with numerous small, rounded, keratotic elevations somewhat larger than pinheads. From the clinical examination a diagnosis of lichen chronica circumscripta was made, but histologically a marked plugging of the sweat pores was observed, which prompted a diagnosis of porokeratosis. Other than the one feature—the plugging of the sweat pores—this case has none of the features of porokeratosis, either macroscopically or microscopically, and undoubtedly is not a true Mibelli's disease. Heidingsfeld made a histologic study of many other conditions, and a similar plugging of the ducts was found in pityriasis rubra pilaris, prurigo, ichthyosis hystrix, clavus, linear nevus and generalized papular dermatitis.

The reports of Hutchins, Gilchrist, Wende and Heidingsfeld complete the bibliography of porokeratosis in the literature of this country,

---

10. Gilchrist: A Case of Porokeratosis (Mibelli) or Hyperkeratosis Eccentrica (Respighi) with a Remarkable Family History. Preliminary Notice, Johns Hopkins Med. Bull. **74**: (May) 1897; Eleven Cases of Porokeratosis in One Family, J. Cutan. Dis. **17**:149, 1899.

11. Wende: Porokeratosis with Report of a Case, J. Cutan. Dis. **16**:505.

12. Heidingsfeld: Porokeratosis Mibelli, J. Cutan. Dis. **24**:29, 1905.

with the exception of one or two publications of foreign writers which will be mentioned later. There is a photograph in Ormsby's [13] "Diseases of the Skin," taken from a case of Montgomery, but no report of this case is made in the literature.

Reisner [14] observed a seasonal variation in the case which he discussed at the inaugural dissertation of the Medical Faculty of Strassburg in 1896. He observed that the lesions were accentuated in summer and attenuated in winter. That there was a true atrophy of the sweat

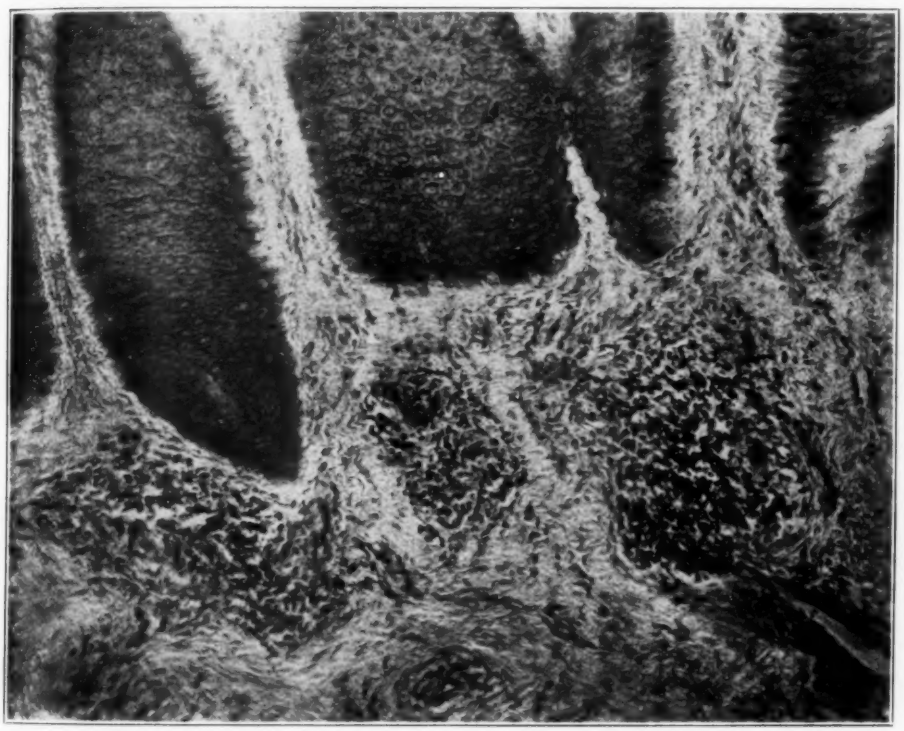

Fig. 6.—Collections of lymphoid cells in subpapillary layer of cutis.

glands in the depressed center, he proved by the fact that sweating was not produced by the administration of pilocarpin.

The first distinct variation in the histology of the condition was brought out in the cases of Joseph.[15] The disease began in the two patients at the age of 3 and 8 years, respectively. He found microscopically that the stratum granulosum was only one or two cells in

13. Ormsby: Diseases of the Skin, Rev. Ed., Philadelphia, Lea & Febiger.

14. Reisner: Ein Fall von Porokeratosis, Inaug. Dissertation von der Medic. Fac. Strassburg, 1896. (Quoted from Respighi).

15. Joseph: Ueber Porokeratosis, Arch. f. Dermat. u. Syph. **39:** 1897.

thickness. In the corium, between the coils of the sweat glands, the mast cells were increased in number and in the epithelium of the glomeruli were numerous karyokinetic figures. He explained these differences from the histology as described by Mibelli as due to the fact that his patients had had the disease only a few years while Mibelli's patient had had it for many years. Mibelli, in a later article, was not inclined to view Joseph's case as a true porokeratosis.

Ducrey [16] and Respighi, at the meeting of the Italian Society of Dermatology and Syphilology in Rome in 1897, announced that they had observed three cases of the disease in which the lesions were on the buccal mucosa. Clinically and histologically these lesions corresponded exactly to those present on the skin except for modifications due to differences in the tissue affected.

Basch,[17] in 1898, reported the case of a man, aged 36, who had had the lesions since the age of 10. Although patches were found on the mucous membrane, they were not studied microscopically. From the histologic study of the skin lesions, the author concluded that the process had its beginning in the epidermis, agreeing with the views of Mibelli, Reisner, Joseph and Gilchrist. A marked degree of pruritus was the only subjective symptom.

Respighi [18] and Ducrey, in a joint monograph, reviewed the former's eleven cases and gave an exhaustive account of the report of other authors. In all of Respighi's patients the skin was affected, in five alone and in six simultaneously with the mucous membranes. In no case was the affection limited to the mucous membrane. The tendency of the disease to appear in several members of the same family was marked in their observations. In only two cases of the eleven did the condition appear in virgin soil, while the remaining nine cases were gathered from three families—two, three and four cases, respectively, from each. Outside of the cases seen and examined personally by the writers, the first family had eight more members similarly attacked, the second and third families one more in each. In no case was the disease transmitted from husband to wife. In the first family all four members were nursed by the same woman. In the lesions on the mucous membranes they found a ridge surrounding a central area, in

16. Ducrey and Respighi: Les localizations sur la muqueuse bucale de l'affection improprement appelée porokeratose, communication to the Ital. Society of Dermat. in December, 1897, published in Annal. de. Derm. et de Syphiligraph, January, 1898, p. 1.

17. Basch: Ein fall von Porokeratosis (Mibelli), Pest. med. chir. Presse, **34**:27, 1898.

18. Ducrey and Respighi: L'Hyperkeratose Figurée Centrifuge Atrophiante, Ann. d. Dermat. et Syph. **9**:609 and 734, 1898.

this way corresponding to skin lesions. However, they described the ridge of the mucous membrane patch as being very thin and never showing a seam in its center. Histologic study of the skin lesions showed that the central area was occupied by the opening of a tubular or acinous gland, by a hair follicle and its sebaceous appendage, or no gland at all was present. The raised seam was formed by modified cells of the malpighian layer and subjacent connective tissue. Respighi and Ducrey thought that the disease might have its origin in the corium rather than in the epidermis. Because of the exceptional clinical char-

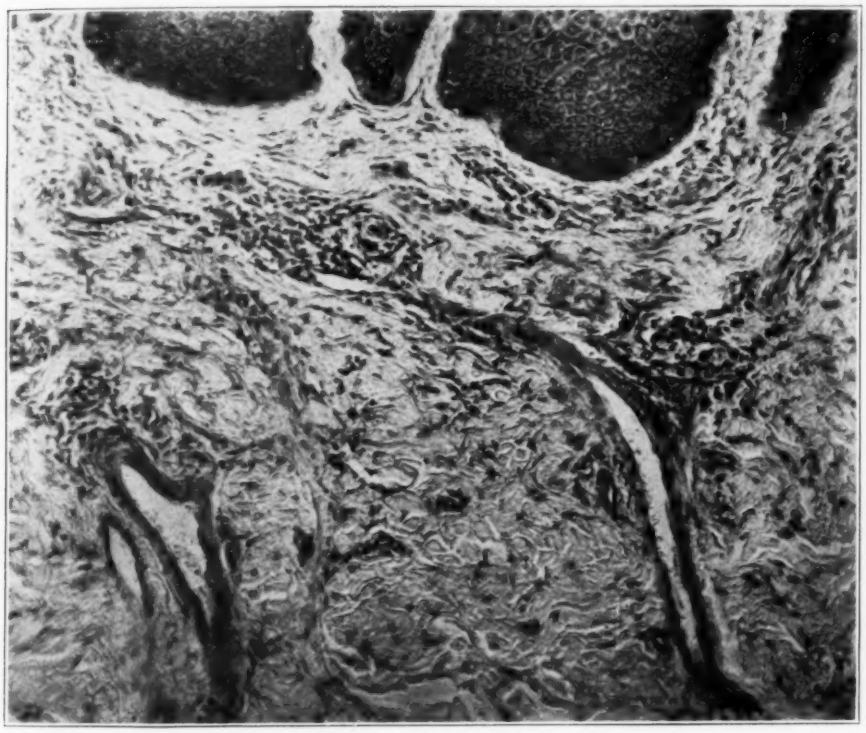

Fig. 7.—Dilated lymph and blood spaces surrounded by lymphoid cells.

acteristics they suggested the name "hyperkeratosis figurata centrifuga atrophicans" instead of "porokeratosis."

Mibelli,[19] in 1899, reported a case in which lesions were found on the glans penis and in the mouth in a patient 68 years old. The disease was of thirty years' duration and occupied the trunk and both extremities. It was traceable through four generations.

19. Mibelli: Ueber einen Fall von Porokeratosis mit Localization in Munde, Arch. f. Dermat. u. Syph. **47**:1, 1899.

Heller,[20] in a report of a single case, told of marked improvement following the use of a salicylic acid and mercury plaster.

The lesions in Wolf's [21] case were absent in winter and appeared each summer.

Between the years of 1900 and 1905 there was very little published concerning porokeratosis. A case of Du Castel and Langlet [22] was thought to be lichen planus by Hallepeau and Darier, the former basing his opinion on the clinical picture and the latter on the histologic findings. Typical lesions of lichen planus were found on the forearms and glans penis. Galloway [23] saw the disease in a girl, aged 17, but made no histologic study. Mantoux's peculiar form of keratosis of the palms and soles, which he entitled "porokeratose papillomatose" had nothing to do with the sweat ducts microscopically, and clinically was not a case of true porokeratosis Mibelli.

Fig. 8.—Late lesion showing depressed center and peripheral walls with depressions corresponding to craters; absence of sweat ducts and follicles in central area; hyperkeratosis, plugging of sweat ducts, acanthosis and inflammatory reaction in cutis in the region of the peripheral wall.

Mibelli,[24] in 1905, reported two new cases. The first occurred in a man of 66 and had been present since early life. The second occurred

20. Heller: Demonstration of a Case, Verhaundlung Berl. Dermat. Gesellsch., Dermat. Ztsch., 1899, p. 671, and Arch. f. Dermat. u. Syph. **47**:435.

21. Wolf: Demonstration of a Case of Porokeratosis, Arch. f. Dermat. u. Syph. **47**:415, 1899.

22. Du Castel and Langlet: Porokeratose, Soc. de dermat., February, 1900; Ann. de dermat. et syph., 1900, p. 228.

23. Galloway: Case Demonstration, London Dermat. Soc., Brit. J. Dermat., 1901, p. 262.

24. Mibelli: Le propos. de deux nouveaux cas de Porokeratose, Ann. de dermat. et syph.., 1905, p. 503.

in a man of 20 and had been present for ten years. His grandfather, father, uncle and two brothers also were affected with the condition. Mibelli places the disease among the incurable dermatoses.

Truffi,[25] writing in the same number of the *Annales*, reported a case in a boy of 13 in whom the lesions had been present since the age of 11 months. In this patient there was a definite grouping of the patches, corresponding to the distribution of peripheral nerves to the affected areas. Thus, he found that a lesion on the face was exactly limited by the median line and occupied, as adjacent patches, the areas innervated by the last two branches of the trigeminal nerve. In this way, the entire eruption could be mapped out according to nerve distribution. Mibelli [26] confirmed Truffi's case to be a true porokeratosis, and in a later article referred to it as a point of confirmation of his first opinion —that porokeratosis should be regarded as a disease beginning in the superficial layers of the skin and having its seat in an alteration of congenital origin. He refers to Truffi's case because of the systematic arrangement, which is common with nevi.

In 1907 cases were reported by Himmel [27] and Brocq and Pautier.[28] The former made a necropsy examination of a case in which the patient died of an intercurrent affection, but was unable to add anything to the knowledge of the condition. The case of the two latter men lacked the seam in the peripheral wall of the lesions, which is one of the chief characteristics of a true Mibelli's porokeratosis. Baum,[29] in 1908, saw lesions distributed along the nerve trunks, and while the case was under observation a new nerve was affected.

Pasini,[30] in 1912, before the International Congress of Dermatology gave a report of twenty-six cases being found in one family. Maki,[31] a Japanese observer, was reminded of systematized nevi by the localization of three cases of this disease. The first two cases occurred in brothers and affected the face, neck, back and legs symmetrically in

25. Truffi: Sur un cas de Porokeratose systematosée, Ann. de Dermat. et syph., 1905, p. 520.

26. Mibelli: A propos. de l'article de Truffi "Sur un cas de porokeratose system," Ann. de dermat. et syph., 1905, p. 595.

27. Himmel: Ein Fall von Porokeratosis, Arch. f. dermat. u. syph. **84**:279, 1907.

28. Brocq and Pautier: Cas de Porokeratose, Bull. Soc. Hôp. de Paris, January, 1907, p. 651.

29. Baum: Porokeratosis Mibelli, Verhandlung Deutsch. Dermat. Gesellsch., June, 1908, Arch. f. dermat. u. syph. **91**:363.

30. Pasini: Demonstration VII International Dermat. Congress, Rome. Dermat. Wchnschr. **55**:1733, 1912.

31. Maki: Three Interesting Cases of Porokeratosis and Its Treatment, Abst. in J. Cutan. Dis., July, 1914; Japan Ztsch. f. Dermat. u. Urol., January, 1914.

both. The third was in a girl, the side of the head being affected. Treatment with roentgen ray, radium, mesothorium, quartz-lamp and carbon dioxid snow was tried out. The best success was attained by the last.

Isaac [32] demonstrated a case in 1913 in which only the scrotum was involved.

Matosumoto,[33] in 1917, reported a case of lesions on the hand in a man, aged 27, consisting of minute horny, conical elevations and slight depressions with comedo-like plugs, which histologically showed hyper-

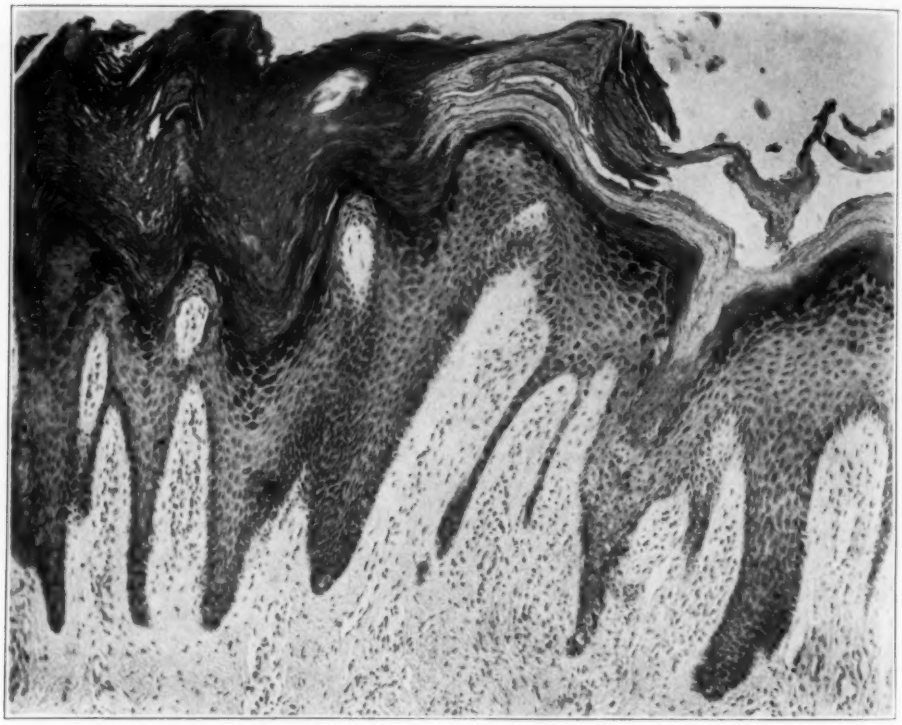

Fig. 9.—Peripheral wall, showing crater and plug in sweat duct.

keratosis over the sweat duct openings. Objectively, there was no peripheral wall and no tendency to eccentric growth. Matosumoto recognized this as a peculiar form of porokeratosis and suggested the name "porokeratosis eccentrica." There is little to recommend this

32. Isaac: Porokeratosis Mibelli, Berl. Dermat. Gesellsch., July, 1913; Ref. Derm. Wchnsch., **57**:981.

33. Matosumoto: A Peculiar Form of Porokeratosis, J. Cutan. Dis. **34**:489, 1916.

case as one of porokeratosis Mibelli, the only analogous finding being the keratosis of the sweat ducts.

McCormac and Pellier,[34] in 1918, reported a case in a man, aged 27, in whom the disease had started at the age of 25. Typical lesions were found on the tongue, and the writers presented this fact as an argument against the sweat duct origin of the disease. Matosumoto's [35] cases, of which he made a brief tabulated report, were more likely cases of linear nevus. Both clinically and histologically they corresponded more closely with the latter disease than with porokeratosis. In all of his cases he found follicular keratosis, and he maintained that the follicles were implicated to the same extent as the sweat ducts. As he was not dealing with a true Mibelli's disease, his observations are of little value. A considerable number of reports from the Japanese literature are included in Matosumoto's bibliography. These cases are unavailable for this study.

Sevenig,[36] in November, 1918, reported a case and discussed the classification of the disease.

In 1914, Sellei [37] reported the case of a man, aged 45 years, who had had the condition since the age of 8. Each year the nails of the toes had dropped off. There were many lesions on the palms and soles.

In April, 1920, Bruck and Hirsch [38] saw a case, examined it clinically and histologically and decided that porokeratosis belonged in the group of nevi. Their report gives a comprehensive review of the literature.

ETIOLOGY

In spite of the numerous theories which have been advanced as to the etiology of this affection and the experimental work that has been directed toward that end, it must still be regarded as entirely unknown. The part that heredity plays cannot be denied. It was first suggested by two of the cases of Mibelli, in which a brother and sister were affected; and was later strikingly illustrated by Gilchrist, who found eleven members in one family with the disease, and Pasini, who saw twenty-six cases in one family. Many other writers have made the same observation, although occasionally a case has been reported in

34. McCormac and Pellier: A Case of Porokeratosis, Brit. J. Dermat. Oct.-Dec., 1918, p. 197.

35. Matosumoto: The So-called Porokeratosis (Mibelli), with Special Reference to Its Histopathology, J. Cutan. Dis., July, 1918, p. 379.

36. Sevenig: Ein Betrag zum Frage der Porokeratosis Mibelli, Dermat. Ztsch., November, 1918, p. 292.

37. Sellei: Ein Fall von Porokeratosis, Dermat. Wchnschr., April, 1919, p. 241.

38. Bruck and Hirsch: Ueber Porokeratosis Mibelli, Dermat. Ztschr., April, 1920, p. 221.

which the family history was entirely negative. The part that heredity plays is well illustrated in our case. The description of the lesions present in the grandmother and father, as set forth by the patient, leaves little doubt that they were typically those of porokeratosis. The daughter was examined personally, and a typical early lesion was found on the left knee. The crater around the border of the lesion was indistinctly visible. The lesion was apruritic.

The original theory of Mibelli was that the lesions came under the classification of nevi, and that they resulted from some congenital cell rests in the skin. Even as late as 1905 he still clung to this belief. Truffi held that the development of the lesions for the first time in a person of 55 disproved such a theory. Lombardo [39] has recorded a brief report of an example of porokeratosis with carcinoma developing in one of the lesions. It is well known that carcinoma frequently develops in nevi, and, according to the theory of Cohnheim, carcinoma is supposed to originate from cell rests. Thus we might argue that the lesions of porokeratosis develop from cell rests, but the analogy is only suggestive. Most recent writers, among them Bruck and Hirsch, favor the nevus theory.

Respighi, in spite of negative experimental work, favored a parasitic theory. Other writers, including Basch and Wende, have attempted to find a parasite, but except for Wende's one successful inoculation into his original patient, all trials have been without results. The success of Wile and Kingery in reproducing molluscum contagiosum and verruca with material ground up and passed through a Berkefeld filter suggested the idea of attempting similar experiments with porokeratosis, and in spite of the unsuccessful attempts of other workers to reproduce the disease, the experiment was carried out. No lesions have ever appeared at the sites of injection. There is nothing to recommend a contagious theory for this disease and much against it. In no case has the wife of a patient having porokeratosis been affected with the disease or vice versa. All attempts at inoculation have been negative; all attempts to grow an organism on various mediums have been without results; and special stains have shown nothing.

In Truffi's case the distribution would suggest probably a neurogenous origin. Each group of lesions was mapped out according to the distribution of a peripheral nerve. This theory was suggested by Respighi in his original article, but denied in the same breath. Other cases, such as Pavlow's, Baum's and Maki's, have favored this suggestion.

---

39. Lombardo: Auf dem Boden einer Porokeratose entwickelndes Epitheliom, Abstr. in Monatsh. f. prakt. Dermat., April, 1908; Gior. ital. d. mal. ven. **6:** 1907.

AGE INCIDENCE

In twelve of thirty cases in which the age at which the first lesion appeared was stated, it began before the age of 10, in eight before 20, in four before 30, and the remaining eight from 30 to 35. From this it may be seen that the affection may begin at any age, but more commonly in the earlier years of life. Our patient had had lesions since infancy, and the father's were present throughout his entire life. The affected daughter at present is 9 and has had the lesion on her leg since infancy.

DISTRIBUTION

There is a distinct predilection for the hands and feet, genitals buttocks and scalp, although it may appear at any site. The percentage of cases in which lesions of the mucous membrane occur is high, though not exactly known, for in some instances they were unrecognized and occasionally were not looked for. The palms and soles are almost invariably free; one or two exceptions to this have been recorded.

PATHOGENESIS

Mibelli, in his first work, laid stress on the constant involvement of the sweat ducts and believed that the disease had its origin in the mouths of the ducts. Respighi, in his simultaneous publication, held that the sweat duct orifices and the follicles shared equally in the process, and that either might be the point of origin. The general histologic picture described by the two authors was almost identical. Subsequent writers agreed on an epidermic origin, either in the sweat ducts or in both the ducts and follicles, until 1898, when Respighi and Ducrey suggested a dermic origin.

The histologic study of many sections from our case shows the follicles and orifices of the sebaceous glands to be as constantly involved and in the same way as the sweat duct orifices. However, it does not seem that one can definitely state that the disease has its origin in these structures. The earliest sections show an acanthosis and a considerable degree of cellular infiltration in the cutis. The hyperkeratosis at this stage is slight and the least striking feature of the microscopic picture. For this reason it would be more justifiable to assume that the origin is either in the thickened prickle cell layer or in the papillary layer of the corium. It is true that the early acanthosis is almost immediately followed by a parakeratosis and plugs reaching down into the follicles and gland orifices, but this feature is no more striking than in many other conditions, as Heidingsfeld's studies showed.

There is other evidence to suggest that the origin is not in the sweat ducts. First, the presence of lesions on the mucous membranes is in every way typical, and they correspond closely to those occurring

on the skin. Second, against such an origin and favoring an origin deeper in the skin is the fact that curettement of the lesions is followed by recurrence, while total excision results in cure.

TREATMENT

In his final case report, Mibelli classified porokeratosis among the incurable dermatoses. The results of other writers in treating the condition would tend to support this view. Complete excision has been found to be successful for individual lesions, as has also carbon dioxid, but both of these methods are impracticable in cases in which the patches cover large areas. Following our patient's entrance into this hospital, the roentgen ray was at once applied to all the lesions, a suberythema dose being used. This dosage was repeated every two weeks until five successive treatments had been given. Other than a slight lessening of the pruritus, there was no change in the condition, which was surprising, considering the rapid involution of verruca and other hyperkeratotic and parakeratotic conditions under the ray. Excision and cautery were then tried and so far have been followed by no recurrence. The extent and localization of the eruption preclude the extensive use of either of these methods in our case.

CLASSIFICATION

Throughout the literature of porokeratosis there has been a great diversity of opinion as to its classification. From a résumé of its clinical and histologic characteristics, it would seem that it might best be placed among the verrucae or the nevi. In favor of the former is the wartlike appearance of the lesions, particularly in the earlier stages. Histologically, the epidermal and papillary hypertrophy and the marked hyperkeratonization correspond to the picture of verrucae. The familial tendency, the persistence of the lesions throughout life, the absence of inflammatory changes, the noncontagiousness, the occasional systematic arrangement and the failure to respond to the roentgen ray speak strongly in favor of the placing of porokeratosis among the nevi. Until the etiology and the point of origin of the lesions are understood, a definite classification is impossible. At the present time it is generally included among the hypertrophies of the skin without any attempt at a more definite grouping. From our study it would seem better placed among the verrucous nevi.

CONCLUSIONS

1. Porokeratosis is a distinct clinical entity characterized by a familial tendency and a characteristic clinical and histologic picture.

2. Clinically it is characterized by the occurrence of elevated, wartlike lesions which, as they enlarge, form an irregular peripheral wall surrounding an atrophic depressed center.

3. Histologically it is characterized first by an acanthosis and by inflammatory changes in the corium, which are rapidly followed by a hyperkeratosis with plugging of the sweat ducts and follicles.

4. Porokeratosis is best classified under the group of verrucous nevi because of the wartlike character of the lesions clinically, the epidermal hypertrophy as observed histologically, the familial tendency, the noncontagiousness, the persistence throughout life, the absence of inflammatory changes, the occasional systematic arrangement and the failure to involute under the ray.

ABSTRACT OF DISCUSSION

Dr. August Ravogli, Cincinnati: I have always considered porokeratosis to be nothing less than a very limited form of lichen. The slight itching sensation and the formation of the small papules which remain for a long time, sometimes for six months or a year, without change, neither increasing nor diminishing, is in favor of this resemblance. The pathologic specimen which Dr. Wright presented looks a great deal like the condition found in pityriasis rubra pilaris, in which there is a slight infiltration in the derma and an increased quantity of epidermis all around the hair follicles and glands. For this reason I have always regarded this disorder to be nothing less than an attenuated and circumscribed condition, probably identical with lichen planus.

Dr. Fred Wise, New York: I have never seen a case. I was particularly pleased with Dr. Wright's classification of the disease as a nevus because those who have studied the disease, taking into consideration the structure, class it as a form of nevus, such as von Recklinghausen's disease and keratosis plantaris and palmaris, and so on. One point that has interested me in looking over the literature of the subject is an article in a Japanese journal in which the author classifies several cases as porokeratosis — cases which I and others to whom I showed the article regard as ordinary linear nevus. In these examples he did not describe any central involution so far as I could ascertain. It is a question in my mind whether those two conditions should be correllated, although we admit that they are both nevi. Porokeratosis and linear nevus should not be classed together. The name porokeratosis should be limited to the lesions with a depressed center and raised acanthotic peripheral wall.

Dr. Carroll S. Wright, Ann Arbor, Mich.: In regard to Dr. Ravogli's suggestion that the disease resembles lichen planus: In going through the literature I found many other cases reported as porokeratosis which on careful study were found to be true cases of lichen planus. However, in our case there were no lesions suggestive of lichen planus, either clinically or pathologically. As to the histologic picture resembling pityriasis rubra pilaris, it is true that it is a disease of the sweat ducts and hair follicles, but this is the only point of resemblance. Heidingsfeld in 1916 made a complete examination of the diseases which he found associated with the sweat ducts and hair follicles. Among these were pityriasis rubra pilaris, porokeratosis and some others. We also reviewed the cases to which Dr. Wise has called attention and thought that they were cases of linear nevus. In no case was there present the central involution which characterizes the late stages of the disease. There was only a slight resemblance to the cases seen in these instances. They are the cases reported by Matsumoto.

XXIV.—IMMUNITY STUDIES IN EXPERIMENTAL SYPHILIS *

II. SPIROCHETICIDAL PROPERTIES OF SERUMS IN LATENT AND EXPERIMENTAL SYPHILIS WITH SOME OBSERVATIONS ON IMMUNITY

FREDERICK EBERSON, PH.D.
ST. LOUIS

INTRODUCTION

The vast amount of literature dealing with the problem of immunity in syphilis may be grouped into a series of extensive clinical observations, on the one hand, and on the other, the report of a considerable amount of experimental work which received its first impulse from the pioneer studies on syphilis transmission in chimpanzees by Metchnikoff and Roux [1] two years prior to Schaudinn's discovery of *Spirochaeta pallida*. The conclusions, which were drawn from both the clinical and experimental data that had accumulated during a period of years, were, in the first instance, the result of observations not subject to control, and, with the causative agent yet unknown, could not be interpreted scientifically; in the second instance, the experimental findings, without exception, were based on what is now known to be an erroneous conception of the nature and behavior of the syphilitic virus within the animal body.

Reinoculation in Syphilis.—From the clinical studies of Levaditi,[2] Neisser,[3] Finger and Landsteiner [4] and others, we reach the conclusions that in the syphilitic patient definite resistance to reinoculation is acquired shortly after the appearance of the primary lesion; that the resistance is manifest throughout the secondary stage and in the tertiary stage in which, however, reinoculation becomes more frequently possible, after a certain time; that susceptibility to reinfection may

*Work done under a partial grant from the U. S. Interdepartmental Social Hygiene Board, Washington, D. C.

* Studies, reports and observations from the dermatological department of the Barnard Free Skin and Cancer Hospital and the Washington University School of Medicine, St. Louis, Mo., U. S. A., service of Drs. M. F. Engman and W. H. Mook.

1. Metchnikoff and Roux: Ann. de l'inst. Pasteur **17**:809, 1903; **18**:1, 659, 1904; **19**:673, 1905; **20**:875, 1906.

2. Levaditi: Ztschr. f. Immunitätsforsch., 1910, Ref., Pt. 2, p. 277.

3. Neisser: Beiträge zur Pathologie und Therapie der Syphilis, Berlin, Julius Springer, 1911.

4. Finger and Landsteiner: Arch. f. Dermat. u. Syph. **78**:335, 1906; **81**: No. 1, 1906.

return even though the syphilis has been entirely cured, although in this regard a difference in degree of susceptibility prevails as compared with the susceptibility of a normal person.

Animal experimentation has led to definite conclusions which are correlated in the main with the earlier clinical observations and indicate a state within the animal body comparable with ideas of immunity expressed in the foregoing, in which progressively increasing resistance is developed as the syphilitic virus becomes generally distributed, until during the early tertiary stage this resistance reaches a maximum. In reviewing the work done by different investigators, we find two distinct points of view expressed. Neisser, for instance, is representative of those who believe that no immunity to syphilis exists, and that failure to reinoculate means an existing syphilis rather than any definite immune condition. In support of this theory he has adduced a number of positive inoculations with emulsions of bone marrow and spleen from monkeys which had resisted a second infection. On the other hand, animals which had been cured by drugs could be reinoculated. Finger and Landsteiner [5] have taken a different view, and much of the later experimental work in syphilis is in accord with their idea that immunity increases gradually with the onset of the disease and becomes absolute during the "second latent period" preceding the tertiary stage when gummatous lesions may be developed. It is to be noted, in this place, that the interpretation of "immunity" phenomena has rested primarily on the principle of resistance which is developed in the host after the syphilitic virus has become generally distributed. This idea, although reasonably consistent with ordinary immunity phenomena, was based, however, on inadequate knowledge.

Localized Reactions and Tissue Immunity.—Early investigations by Metchnikoff, Roux, and Neisser had brought out the fact that experimental syphilis in monkeys gave rise to immune properties of the skin similar to that found in man; that is, reinfections were not possible at a time when a primary lesion was manifest. In confirming these observations an attempt was made by Kraus and Volk [6] to explain the paradoxic reaction in persons with generalized syphilis in whom cutaneous infections could rarely, if ever, be elicited by reinoculation. It appeared that resistance developed slowly and was at its height only after a long time. Superinfections were possible up to about three weeks after the first inoculation and prior to the appearance of a primary lesion. Reinfection failed, as a rule, after the lesion had persisted for several days. Under these conditions superinfections were characterized by

5. Finger and Landsteiner: Verhandl. d. deutsch. Dermat. Gesellsch., IX Kongress, Springer, 1907, p. 25.

6. Kraus and Volk: Wien. klin. Wchnschr. **19**:621, 1906.

their relatively benign appearance and much smaller size as compared with the ordinary initial lesion. That the size and type of lesions may be influenced by preexisting ones has been mentioned by Nichols,[7] and Brown and Pearce [8] in later studies. The possible influence of primary foci on the subsequent development of later lesions had already been suspected by Kraus and Volk,[6] and in a few of their experiments rudimentary manifestations were observed when lesions were excised from seven to fourteen days after their appearance. From this it was concluded that a skin immunity appeared to prevail in the same degree as before and that a partial immunity seemed to develop as a result of inoculation of the surface of the skin. An explanation of the previously described phenomenon of resistance to reinfection by way of the skin and mucous membrane at a time when certain organs and tissues continue to undergo injury must be sought for in the behavior of certain tissues, such as the rabbit testicle, for example. It has been found that apparent recovery from a previous lesion develops a resistance to subsequent inoculation, although ordinarily no generalized resistance in rabbits appears to develop during the disease, since the opposite testicle can be successfully inoculated before, during and after the existence of a lesion on the other side. Observations of many investigators point to the probability of a localized reaction existing in the animal body, in consequence of a mechanism by which active invasion with *Spirochaeta pallida* leads to a state of nonsusceptibility. Neisser has called this condition "Anergie." It is conceivable that organisms which may gain entrance at this time may remain uninjured and yet be capable of setting up lesions in other parts of the body. There is evidence from recent studies on the dissemination of *Spirochaeta pallida* and the so-called "carrier state" in latent syphilis that such may be the case. At all events, it seems to be of some importance to differentiate between the classic conception of immunity to syphilis and the state of affairs which is probably more consistent with present-day knowledge of infection with this disease.

Our own investigations in latency in man [9] and in experimental syphilis, together with the observations of Brown and Pearce,[10] have

7. Nichols, Henry J.: Observations on the Pathology of Syphilis, J. A. M. A. **63**:466 (Aug. 8) 1914.

8. Brown and Pearce: J. Exper. M. **32**:445, 1920.

9. Eberson, F., and Engman, Martin F.: An Experimental Study of the Latent Syphilitic as a Carrier, J. A. M. A. **76**:160 (Jan. 15) 1921. Eberson, F.: Dissemination of Spirochaeta Pallida in Experimental Syphilis, Arch. Dermat. & Syph. **3**:111 (Jan.) 1921; XXIII.—Immunity Studies in Experimental Syphilis. Infectivity and Survival of Spirochaeta Pallida in Rabbits, with Observations on Some Strains from Latent Syphilis, Ibid. **3**:775 (June) 1921.

10. Brown, W. H., and Pearce, L.: Note on Dissemination of Spirochaeta Pallida from Primary Focus of Infection, Arch. Dermat. & Syph. **2**:470 (Oct.) 1920.

established the significance of the lymphatic glands as foci from which *Spirochaeta pallida* may be discharged. The rôle which this type of localization may play in immunity may be conjectured. It is not mere speculation to attribute an immunity response to the presence of these organisms since we know that resistance to reinoculation is associated with the presence of spirochetes in some part of the body. Foci in which "latent" spirochetes are localized may act as centers from which antibodies are slowly elaborated and then discharged into the blood stream. From a consideration of an extreme type of localization, such as that found in glands, we next pass on to a study of the immunity phenomena which may be seen to occur in single lesions.

Local Lesions and Inhibitory Effects on Development of Lesions Elsewhere.—Some of the early experiments made with monkeys demonstrated the inhibitory effect exercised by lesions in one organ on the development of lesions in other parts of the body (Metchnikoff and Roux). Using the rabbit testicle for his study, Nichols [7] found that unilateral inoculation when followed by castration of the infected testicle promptly gave rise to lesions in the opposite testicle. The fundamental importance of these observations has led to intensive study of the cyclic changes in syphilis and to those factors which tend to shed much light on immunity reactions in the experimental animal. From the standpoint of immunity response to infection it would be of great value to interpret types of lesions as evidence of a certain kind of reaction, although the change in the character of lesions makes such interpretation difficult. There is evidence, however, that resistance of the animal to *Spirochaeta pallida* is intimately connected with the nature and extent of the reaction taking place at the site of inoculation, and any influence which is capable of modifying the reaction might be expected, according to Brown and Pearce,[11] to react on the phenomena of the infection as a whole. In their opinion, generalization is the measure of resistance. The protection which is developed from any given focus may not affect all tissues or all parts of the body to the same degree, but it may be extended progressively from primary lesions to the successive groups of tissues and manifest protective action in one group at a time when other groups of tissues may be afforded little or no protection. The fact that tissue immunity may manifest itself by extension from group to group has direct bearing on the view which we have expressed regarding the elaboration of antibodies by way of localized areas into the blood stream.

---

11. Brown, W. H., and Pearce, L.: Experimental Production of Clinical Types of Syphilis in the Rabbit, Arch. Dermat. & Syph. **3**:254 (March) 1921.

Cyclic Reactions in Syphilis and Analogous Phenomena of Trypanosome and Spirillary Diseases.—Cyclic phenomena in syphilis find a counterpart in other diseases which are caused by spirochetes. In relapsing fever the periodic functioning of a protectve mechanism is known to take place in the blood of infected individuals, or as Levaditi [12] believes, to manifest itself as a phagocytic reaction which is independent of serum properties. African tick fever offers analogous phenomena, and although recurrences are more common, susceptible animals are immune for a period following a second attack. A similar immunity follows recovery from spironematosis in geese and other fowls. The mechanism on which such immunity depends has been studied by numerous investigators, notably by Gabritschewsky,[13] Marchoux and Salimbeni,[14] Levaditi,[12] Levaditi and Manouelian,[15] Mesnil and Nicolle,[16] Neufeld and von Prowazek,[17] and others. To Gabritschewsky we owe our knowledge of the bactericidal content of blood in relapsing fever in which the protective property was found to be at a maximum after the crisis, diminished during apyrexia and increased again during the next attack. Notwithstanding these fluctuations, immunity as a whole increased in the course of the disease. The protection afforded by active immunity in these different diseases is not wholly dependent on bactericidal properties in the serum, for as Novy and Knapp [18] have pointed out, other immune bodies may play an important part in the mechanism of defense. More recently Inada and his collaborators [19] demonstrated in the blood serum of patients with Weil's disease the presence of a specific lysin for the spironema. Immune bodies may be present four years or more after the attack of disease.

In diseases caused by trypanosomes the facts are similar to those given in regard to spirochete infections. The attributes common to all of these seem to be a resistance to reinfection which coexists with the presence of the living organisms in the host. Syphilis in this respect is analogous in its behavior, not only from the standpoints which have been discussed, but also in regard to certain localizing characteristics of *Spirochaeta pallida* and the reactions attending their dissemination.

---

12. Levaditi: Compt. rend. Soc. de Biol. **60**:134, 1906; Ann. de l'inst. Pasteur **20**:41, 1906.
13. Gabritschewsky: Ann. de l'inst. Pasteur **10**:629, 1896.
14. Marchoux and Salimbeni: Ann. de l'inst. Pasteur **17**:569, 1903.
15. Levaditi and Manouelian: Ann. de l'inst. Pasteur **20**:593, 1906.
16. Mesnil and Nicolle: Ann. de l'inst. Pasteur **20**:513, 1906.
17. Neufeld and von Prowazek: Centralbl. f. Bakteriol. Ref., Abt. 1 **41**:754, 1908.
18. Novy and Knapp: J. Infect. Dis. **3**:291, 1906.
19. Inada, Ido et al: J. Exper. M. **33**:377, 1916.

Analogies may be found again, for example, in diseases of fowls in which *Spirochaeta gallinarum* has been shown to localize in certain viscera and to enter the blood stream by way of diverse glandular tissues.[15]

In weighing the analogy of syphilis to other diseases, one must not lose sight of the fact that the ordinary conception of immunity defines a condition which is the result of a refractory state incompatible with the existence of the organism causing the disease. From the biologic point of view, the cycle in syphilis would tend to disprove the theory that immunity is not possible at any stage of the infection.

EXPERIMENTAL IMMUNITY IN SYPHILIS

Antibody Phenomena.—Serologic studies in experimental syphilis have been concerned mainly with the development in serums of agglutinating and complement-fixing bodies. Attempts to demonstrate specific agglutinins in human and experimental syphilis were made by Hoffmann,[20] Landsteiner and Mucha,[21] Hoffmann and von Prowazek,[22] Uhlenhuth and Mulzer,[23] Metchnikoff and Roux,[1] and others, with negative or indecisive results. Following Noguchi's discovery, in 1911, of a method for isolating *Spirochaeta pallida* in pure culture, he was able to demonstrate in immunized rabbits the presence of agglutinins and complement-fixing substances for cultivated strains. The first successful experiments were reported by Kolmer [24] and were followed soon afterward by those of Nakano [25] and Kissmeyer.[26] With pure cultures of the spirochetes it was possible to develop highly agglutinating serums from rabbits. Serums from individuals in the primary, secondary and tertiary stage and from congenital syphilis were found to contain agglutinins in about 50 per cent. of the cases. These antibodies were shown to be present in highest concentration during the later stages of the disease and in the greatest percentage of cases among persons who showed late primary, secondary, tertiary and latent syphilis (Kolmer, Broadwell and Matsunami [27]). That the reactions of culture *Spirochaeta pallida* differed from those which were obtained from human lesions was next shown by Zinsser, Hopkins and McBurney,[28]

20. Hoffmann: Dermat. Ztschr. **13**:561, 1906.
21. Landsteiner and Mucha: Centralbl. f. Bakteriol., Ref. **39**:540, 1907.
22. Hoffmann and von Prowazek: Arb. a. d. k. Gsndhtsamte **37**:205, 1911.
23. Uhlenhuth and Mulzer: Arb. a. d. k. Gsndhtsamte **33**:183, 1909.
24. Kolmer: J. Exper. M. **18**:18, 1913.
25. Nakano: Arch. f. Dermat. u. Syph. **116**:265, 1913.
26. Kissmeyer: Deutsch. med. Wchnschr. **41**:306, 1915.
27. Kolmer, Broadwell and Matsunami: J. Exper. M. **24**:333, 1916.
28. Zinsser, Hopkins and McBurney: J. Exper. M. **23**:341, 1916.

in a study of agglutinins in serums from animals immunized with culture spirochetes.

Protective Properties of Serum in Human and Experimental Syphilis.—Few references are found in the literature pertaining to protection experiments made in vitro and in vivo with serums from persons or infected animals. Metchnikoff and Roux found serums from monkeys which had been systematically treated with attenuated syphilitic virus ineffective in preventing animal infection with material obtained from active lesions. They believed, however, that they had demonstrated in two instances a definite protective antibody in serum from a monkey which had received subcutaneous injections with syphilitic blood for a period of eight months. A chimpanzee that had been inoculated with a mixture of such serum and material from a chancre remained negative for thirty-eight days, when death from pneumonia supervened. Another monkey, inoculated similarly, evidenced slight lesions as compared with a control. These results appear to be indecisive. Two therapeutic experiments with serums from infected monkeys, reported by Finger and Landsteiner, cannot be interpreted owing to the technic employed. Local subcutaneous injections of serum in a total amount of 59 c.c. failed to prevent roseola which developed eight weeks after primary genital lesions. In both patients the primary lesions were excised previous to administration of the serum. The generalization which follows as a result of extirpation of the primary foci would tend to mask the result of these therapeutic measures.

Spirocheticidal activity of serums has been studied in rare instances. Finger and Landsteiner [5] reported negative results with serums from florid stages of syphilis. In vitro experiments, described by Zinsser and Hopkins,[29] demonstrated spirocheticidal properties for culture strains in the serum of rabbits and sheep that had been immunized with cultures of *Spirochaeta pallida*. With virulent spirochetes obtained directly from lesions, this protective property was not manifested by serum produced with culture spirochetes.[28] These results were confirmed by Noguchi,[30] who found, in addition, that serum from a syphilitic rabbit destroyed culture spirochetes.

EXPERIMENTAL

The experiments which are reported in this paper have been based on the idea that syphilis may offer immunity phenomena analogous or similar to those that are found in other infections which tend to assume a latent or carrier state. In order that the nature of a protective mechanism might be studied more effectively and be subject to control,

29. Zinsser and Hopkins: J. Exper. M. **23**:323, 1916.

30. Noguchi: J. Exper. M. **25**:765, 1917.

the method of experimental infection was designed so as to permit a study of serum properties at different stages of the disease. These animal experiments were planned to supplement the data which might be obtained from an investigation of serums taken from persons having latent syphilis. The protective property of specimens of serums was measured by the presence or absence of spirocheticidal activity when combined with living, virulent *Spirochaetae pallidae* derived from active syphilitic lesions in rabbits. It is recognized that there is great difficulty in determining an effective combination of dosage of spirochetes, volume of serums, time of incubation and the amount of the mixture to be injected finally as a test of antibody content. Since no attempt was made to minimize the chances of infecting the experimental animal, this should be borne in mind when weighing the negative results in which the given stage of infection might have a direct bearing on the protective property of such serum as was used in the test. Detailed quantitative procedures that would measure different degrees of spirocheticidal activity against diminishing doses of virulent organisms could not be followed owing to lack of space and material. The numerous control experiments in which normal serums were used against fixed doses of spirochetes in a manner comparable with the test serums in all particulars were the criteria in every series.

Material and Scope of Experiments.—A study was made of the spirocheticidal property of different serums from patients known to have latent syphilis with a history of old as well as more recent infection, and from experimentally infected rabbits. In the group of animal experiments a considerable amount of material was available for the study of protective serum properties during the various stages of syphilitic infection. The patients who were selected for study were free from visible syphilitic manifestations or symptoms and were for the most part untreated cases.

Technic.—Blood from patients was drawn with sterile precautions by means of a glass syringe from the median vein of the arm. Specimens were allowed to stand at room temperature until the clot was formed and then kept in the ice chest for one half hour before centrifugation. The clear serum was next heated at 54 C. for twenty minutes and stored in hermetically sealed tubes until needed. Serum was from one to four weeks old and never exceeded six weeks at the time experiments were made. Experimentally infected rabbits were bled from the heart, under ether anesthesia, and the serum treated similarly to that which was obtained from patients. Rabbit serums were from two to five weeks old at the time tests were made.

A combined in vitro and in vivo method was used in determining the spirocheticidal activity of serums which were combined in amounts

of 2 c.c. with 0.1 c.c. of a suspension of virulent *Spirochaeta pallida*. The mixtures were incubated in a water bath at 37 C. for one and one half hours and then injected intratesticularly into normal rabbits, in duplicate series for each strain of spirochetes which were used in the test. Normal human and normal rabbit serums served as controls and were subjected to every step in the technic in parallel with the test serums.

Animals Used.—Medium-sized gray and brown rabbits with well developed testicles were used. At the time of inoculation the animals were from 5 to 6 months old, as a rule.

Strains of Spirochaeta Pallida Used.—Three strains of *Spirochaeta pallida* were isolated originally from a penile chancre (No. 170), the gland of a patient with latent syphilis (No. 137) and from the semen of a patient with latent syphilis (No. 117), respectively. Spirochetolytic properties of serums from the latent cases were studied against at least two strains and in some instances with three. Of these strains, No. 170 was used constantly along with either the latent strain No. 137 or No. 117. In this place mention may be made of the fact that no difference in the protective property of the serum was found to exist for any special organism. When definite spirocheticidal activity was present, all of the strains failed to infect, irrespective of their origin. This was not the general rule, however, with serums that were taken from experimentally inoculated rabbits, as will be shown later. Emulsions of *Spirochaeta pallida* were prepared from testicular lesions in rabbits with active syphilis. The strains were transferred from animal to animal at stated intervals and were uniformly and constantly virulent. A small amount of material was taken directly from the lesion by means of a finely drawn out capillary glass pipet. Warm salt solution was added in a small volume to the testicular puncture fluid which was expelled into a sterile Petri dish with the aid of a rubber nipple attached to the pipet. A sterile glass rod, flattened at one end and bent at a convenient angle, was used to grind up the sticky mass in the smallest possible volume of solution. This was next drawn up into a pipet through a thin layer of sterile absorbent cotton placed in the homogenous emulsion. The perfectly clear fluid containing the organisms free from any tissue or foreign material was finally added to the serum and the protective property next studied. Suspensions of this material averaged from 15 to 20 spirochetes per microscopic field.

The rabbits were examined daily after two weeks had elapsed. The testicles of animals that remained negative for two months or longer were punctured at different intervals and dark-field examinations made of the testicular fluid over a period of six months. In a number of instances such animals were anesthetized and the emulsions of testicle,

liver and spleen, and in some cases the inguinal glands were injected into a series of normal rabbits to ascertain the fate of *Spirochaetae pallidae* which were introduced with the serums. At no time were these subinoculations into the testicle successful, showing that those animals were negative which failed to develop lesions synchronously with or approximately at the time the control animals were found positive.

RESULTS OF EXPERIMENTS WITH HUMAN SERUMS

Eighteen specimens of blood serum from persons having latent syphilis were found to have spirocheticidal properties for different strains of *Spirochaeta pallida*. In those cases in which true latency did not exist, no protection was manifested by the serum. A history of recent infection invariably confirmed the experimental results in these instances.

TABLE 1.—RESULTS IN EXPERIMENT 1.

Serum	Amount c.c.	Spirochete Suspension c.c.	Strain of S. pallida	Result
H. Mc. D.....	2.0	0.1	170, 137	Negative; animals remained well
W. M.....	2.0	0.1	170, 137, 117	Negative; animals remained well
H. A.....	2.0	0.1	170, 117	Negative; animals remained well
H. B.....	2.0	0.1	170, 137	Negative; animals remained well
J. A.....	2.0	0.1	170, 137	Negative; animals remained well
C. B.....	2.0	0.1	170, 117	Negative; animals remained well
Normal human..	2.0	0.1	170, 137, 117	Positive lesions after 28, 34, 36 days
Normal rabbit...	2.0	0.1	169, 170 137, 117	Positive lesions after from 4 to 5 weeks, on the average

In Experiment 1 are tabulated the results which were obtained with serums from persons whose infection dated back from three to twenty-five years. The blood Wassermann reactions in these and succeeding protocols refer to specimens which were taken just prior to the experiment, unless specified otherwise.

Clinical Data.—M. Mc. D., a man, aged 55, gave a history of a primary lesion twenty years ago. The history as to antisyphilitic treatment was vague. His wife had had one stillbirth. The blood Wassermann reaction was + + + +.

W. M., a man, aged 45, gave a history of a penile chancre twenty-five years ago. The blood Wassermann reaction was + + + + in the cholesterin antigen. There was clinical evidence of hepatic cirrhosis.

H. A., a man, aged 32, had had a chancre eight or nine years ago, with secondary eruption at the time. The blood Wassermann reaction was + + + +.

H. B., a man, aged 29, gave a history of a chancre on the penis five years ago. His wife had had no miscarriages. The blood Wassermann reaction was + + + +.

J. A., a man, aged 26, had had a chancre four or five years ago, with no eruption at the time. The blood Wassermann reaction was + + + + in the cholesterin antigen and + in the noncholesterin antigen.

C. B., a man, aged 31, gave a history of a chancre three years ago. There was no eruption at the time. His wife had had no miscarriages. The blood Wassermann reaction was + + + + in the cholesterin antigen and + + in the noncholesterin antigen.

The next experiment illustrates the spirocheticidal activity in serum from a patient who had received antisyphilitic treatment until the Wassermann reaction was persistently negative. Another interesting observation brought out in this series is that spirocheticidal bodies may be present in the serum of an infant in common with those present in the mother's serum.

Clinical Data.—M. W., a woman, aged 45, had been taking antisyphilitic treatment for an indefinite period up to about fourteen months prior to the time her serum was obtained for the experiment. Her blood Wassermann reactions were successively negative at intervals of six months and she was classified as "serologically well."

TABLE 2.—RESULTS IN EXPERIMENT 2.

Serum	Amount c.c.	Spirochete Suspension c.c.	Strain of S. pallida	Result
M. W.....	2.0	0.1	170, 137	Negative; animals remained well
M. L. D.....	2.0	0.1	170, 137	Negative; animals remained well
D. L. D.....	2.0	0.1	170, 137	Negative; animals remained well
Normal rabbit	N. 2.0	0.1	170, 137, 117	Positive lesions after 4 to 7 weeks
Normal human..	2.0	0.1	170, 137, 117, 169	Positive lesions after 4 to 7 weeks

M. L. D., a woman, aged 34, gave no history of infection and had received no treatment. Her blood Wassermann reaction was + + + + in the noncholesterin antigen.

D. L. D., a girl, aged 18 months, whose mother is M. L. D., gave a + + + + Wassermann reaction in the noncholesterin antigen only. She was apparently healthy and free from syphilis.

Typical cases of latent syphilis are those in which the patient has no history of an infection, no history of treatment for syphilis at any time, and in which there are no signs or manifestations of the disease. Such persons usually find their way to the clinic for syphilis by way of other clinics to which they may have come for examination. These patients, as a rule, give a positive blood Wassermann reaction in one antigen only, generally the cholesterin antigen. The following experiment which was performed with such a group of patients gave uniform results for spirocheticidal properties in the serums tested.

Clinical Data.—R. C., a woman, aged 31, gave no history of infection, and the patient had never taken any treatment. The blood Wassermann reaction was + + + + in the noncholesterin antigen only.

R. O'N., a woman, aged 33, gave no history of infection. She had had two miscarriages. The blood Wassermann reaction was + + + + in the cholesterin antigen only.

G. B., a woman, aged 33, gave no history of infection or treatment. The blood Wassermann reaction was + + + + in the cholesterin antigen only.

A S., a woman, aged 27, gave no history of infection or treatment. The blood Wassermann reaction was + + + + in the cholesterin antigen only.

TABLE 3.—RESULTS IN EXPERIMENT 3.

Serum	Amount c.c.	Spirochete Suspension c.c.	Strain of S. pallida	Result
R. C.	2.0	0.1	170, 137, 117	Negative; animals remained well
R. O'N.	1.5	0.1	170, 137	Negative; animals remained well
G. B.	1.5	0.1	170, 117	Negative; animals remained well
A. S.	2.0	0.1	170, 117	Negative; animals remained well
Normal human	2.0	0.1	170, 137, 117	Positive lesions after 29, 32 and 35 days, respectively
Normal rabbit	2.0	0.1	170, 137, 117	Positive lesions after 30, 28 and 30 days, respectively

In Experiment 4 are summarized the results of protection tests for another group of patients who gave no history of infection and whose blood Wassermann reactions were positive in both antigens, or, as in the majority of cases, slightly positive in either one or the other in inverse relationship.

TABLE 4.—RESULTS IN EXPERIMENT 4.

Serum	Amount c.c.	Spirochete Suspension c.c.	Strain of S. pallida	Result
S. S.	2.0	0.1	170, 137	Negative; animals remained well
J. S.	2.0	0.1	170, 137	Negative; animals remained well
E. O'N.	2.0	0.1	170, 137, 117	Negative; animals remained well
L. C.	2.0	0.1	170, 117	Negative; animals remained well
S. W.	2.0	0.1	170, 137, 117	Negative; animals remained well
Normal human	2.0	0.1	170, 137, 117, 169	Positive lesions after 4 to 6 weeks
Normal rabbit	2.0	0.1	170, 137, 117, 169	Positive lesions after 4 to 6 weeks

Clinical Data.—S. S., a man, aged 28, gave no history of infection. The blood Wassermann reaction was + + + + in the cholesterin antigen and + + in the noncholesterin antigen.

J. S., a woman, gave no history of infection, and her husband's blood Wassermann reaction was negative. The blood Wassermann reaction of the patient was + + + +.

E. O'N., a woman, gave no history of infection or eruption, and there had been no miscarriages. The patient came to the clinic for trigonitis. The blood Wassermann reaction was + + + + in the cholesterin antigen and + in the noncholesterin antigen.

L. C., a woman, gave no history of infection or eruption. She had had one miscarriage. The blood Wassermann reaction was + + + + in the cholesterin antigen and + in the noncholesterin antigen.

S. W., a man, aged 30, gave no history of infection. His wife and only child were well and free from syphilis. The blood Wassermann reaction was + + + + in the cholesterin antigen and + in the noncholesterin antigen.

THE BLOOD SERUM IN EARLY SYPHILIS AND THE LATENT STAGE OF RECENT INFECTIONS

The presence of a protective property in serums from cases of syphilis would seem to depend on the stage of infection. A difference is to be noted between latency in the sense defined as occurring after a very old infection and the period of latency which occurs early in the disease and as an interval between the possible flaring up of a train of typical symptoms.

The serums from a group of seven patients with histories of recent infection were found uniformly negative for spirocheticidal activity. These results were in marked contrast to those obtained in the other series, and are summarized in Experiment 5.

TABLE 5.—RESULTS IN EXPERIMENT 5.

Serum	Amount c.c.	Spirochete Suspension c.c.	Strain of S. pallida	Result
L. M.	2.0	0.1	170, 137	Positive lesions after 32 to 38 days
D. W.	2.0	0.1	170, 137	Positive lesions after 40 to 44 days
J. B.	2.0	0.1	170, 117	Positive lesions after 48 to 50 days
E. L.	2.0	0.1	170, 137, 117	Positive lesions after 50 to 52 days
C. W.	2.0	0.1	170, 117	Positive lesions after 38 to 40 days
F. B.	2.0	0.1	170, 137	Positive lesions after 55 to 57 days
N. N.	2.0	0.1	170, 137	Positive lesions after 42 to 44 days
Normal human	2.0	0.1	170, 137, 117, 169	Positive lesions after 40 to 42 days
Normal rabbit	2.0	0.1	170, 137, 117, 169	Positive lesions after 36 to 40 days

Clinical Data.—L. M., a woman, aged 32, had had two miscarriages. Her history as to infection was vague. She showed definite signs of active pulmonary tuberculosis. The blood Wassermann reaction was + + + + in both antigens.

D. W., a man, aged 39, gave no history of infection. The blood Wassermann reaction was + + + + in the cholesterin antigen. The patient gave clinical evidence of prostatitis.

J. B., a man, had had a primary lesion on the penis two months ago. The blood Wassermann reaction was + + + + in both antigens.

E. L., a man, aged 30, gave a history of infection eight months ago with a + + + + blood Wassermann reaction at the time. Two months later the reaction was + + + + in the cholesterin antigen. One month afterward, following two weeks of mixed treatment, the reaction was +; a month later it was again + + + +. At the time a specimen of serum was taken for the experiment the Wassermann reaction was negative.

C. W., a man, aged 24, gave a history of a primary sore on the penis two years ago. He had taken three injections of arsphenamin at the time. The blood Wassermann reaction was ++++.

F. B., a woman, gave no history of infection. She had had two recent miscarriages. Her husband had been taking antisyphilitic treatment. The blood Wassermann reaction was ++++ in the cholesterin antigen and ++ in the noncholesterin antigen.

N. N., a woman, gave no history of infection or miscarriages. She had been "feeling ill" for the past two years coincident with her husband's infection which dated back to that time. He had been taking treatment for syphilis during the past year. The patient's Wassermann reaction was ++++ in both antigens.

This series illustrates that there may be a complete correlation between the presence of protective substances in the serum and the stage of the infection. Where true latency has been attained by the individual, the serum exerts a spirocheticidal effect on *Spirochaeta pallida*. On the other hand, where the disease has not yet become latent and where an active focus appears to exist, the serum seems to be devoid of spirocheticidal properties. In one instance an acute infection coexisted with syphilis, so that it is difficult to interpret the result. An intercurrent infection may vitiate the effective functioning of any existing serum properties even in those persons who may be "latent" cases.

PROTECTIVE PROPERTY OF SERUM IN RELATION TO THE WASSERMANN REACTION OF THE BLOOD

No attempt will be made to discuss the matter of antisyphilitic treatment and the measure of its efficiency in terms of the Wassermann reaction, or to evaluate the possible effects which any treatment may have on the natural immunity response to the invading *Spirochaeta pallida*. It is clear from the foregoing experimental study that a negative Wassermann reaction following treatment for syphilis may or may not go hand in hand with spirocheticidal activity of the serum in question. It is equally clear that continued treatment which renders a Wassermann test repeatedly negative does not nullify any protective property which may be present in the serum. The important point is that spirocheticidal activity of serum, irrespective of the Wassermann reaction, is essentially a function of time and depends on the degree to which the individual has elaborated and distributed the slowly accumulating antibodies. A negative blood Wassermann reaction attending treatment of a recent infection is not comparable to a similar result in the case of a person whose infection is of older origin. In the one instance we may find no spirocheticidal serum properties and in the other we may. A temporary negative Wassermann reaction must not be confused with one which is repeatedly negative and in

accordance with which a treated patient may be classified as "serologically well." These points are illustrated in Experiment 2 (M. W.) and in Experiment 5 (E. L. and C. W.).

SPIROCHETICIDAL SERUM AND ITS EFFECT ON THE DISSEMINATION OF SPIROCHAETA PALLIDA

Spirochaetae pallidae are discharged into the blood stream early in the course of infection from a primary focus. The organisms may be recovered from the regional lymph glands or the blood stream as early as forty-eight hours after experimental inoculation and may be present for an indefinite period up to and including the first signs of infection (Brown and Pearce,[11] Levaditi [12]).

An experiment was planned with a view to determine the effect of a possible spirocheticidal reaction within the rabbit testicle on the dissemination of *Spirochaeta pallida*. The animals which were used in this group were selected at random from one of the series at a time

TABLE 6.—SUMMARY OF EXPERIMENT 6

Aug. 14, 1920 Series A Rabbit		Sept. 4, 1920 Series B Rabbit
336	2 c.c. blood →	353 and 354
337	2 c.c. blood →	355 and 356
338	2 c.c. blood →	357 and 358
339	2 c.c. blood →	359 and 360

when the outcome as to spirocheticidal activity of the serums under test was not known. The results were decisive, although the series was not large.

Experiment 6.—Rabbits were injected intratesticularly with mixtures of serums and virulent *Spirochaeta pallida* to determine the presence of protective substances in the specimens. Twenty-one days later, these animals were bled from the heart under ether anesthesia and 2 c.c. of defibrinated blood injected immediately into the testicles of normal rabbits in duplicate series. The subinoculated animals were examined regularly over a period of six months, during which time repeated testicular punctures were made in order to check up the examination. Table 6 is a summary of the experiment.

Results of Inoculation.—Oct. 18, 1920, Rabbit 339 presented a small bean-sized nodule in the testicle. Dark-field examination showed enormous numbers of *Spirochaetae pallidae*. Jan. 6, 1921, rabbits 359 and 360 developed pea-sized nodules in the upper pole of the testicle. Dark-field examination showed enormus numbers of *Spirochaetae pallidae*.

The other animals in both series remained uniformly and persistently negative. When injection with a mixture of spirocheticidal serum and spirochetes resulted in negative inoculations, the blood from these rabbits proved to be free from *Spirochaeta pallida*. When protective action was not manifested by the serum, dissemination occurred in the usual manner. The conclusion, therefore, is that spirocheticidal activity of serum in latent syphilis is of such a character as to prevent the normal dissemination of spirochetes from the primary focus.

THE BLOOD SERUM IN EXPERIMENTALLY INFECTED RABBITS

The rabbit serums which were studied for spirocheticidal properties were obtained from experimentally infected animals at different times after inoculation. Four strains of *Spirochaeta pallida* were used in these experiments. Two were isolated originally from two cases of latent syphilis—from the inguinal gland and semen, respectively—and two were isolated from penile chancres. The strains from latent sources are designated as No. 137 and No. 117, respectively, and the chancre strains as No. 169 and No. 170.

Serums containing suspensions of *Spirochaeta pallida* were injected into a series of normal rabbits in accordance with a combined in vitro and in vivo method which has already been described. Homologous and heterologous strains of spirochetes were used in making spirocheticidal tests. For controls, normal rabbit serums were used and also a number of test serums to which no *Spirochaeta pallida* had been added. The results with the different serums are grouped according to the time after infection when specimens were taken. There is indicated also the number of days which elapsed between the last positive dark-field examination of such infected rabbits and the date when serum was obtained. All subinoculated series of rabbits were kept under observation for from three to four months, during which time repeated testicular punctures and dark-field examinations were made, irrespective of the absence of any lesions.

The experiments are summarized in the following manner: Spirocheticidal activity was developed in the rabbit in the course of from six months to one year after the original infection. During the time that spirochetes were found in lesions and for a certain period during which dark-field examinations yielded persistently negative results, the serum was devoid of protective elements. Strains of *Spirochaeta pallida* from latent sources appeared to develop an immune serum having a wider range of protective action. Whereas such serums exerted spirocheticidal action toward heterologous as well as homologous strains of spirochetes, the serums obtained from rabbits which were inoculated with chancre strains failed to protect against inoculation with heterologous strains, even when the time which had elapsed since infection was comparable to that in the other series of animals (Experiment 3).

Experiment 7.—In this series, the strain of *Spirochaeta pallida* used was isolated from the inguinal gland of a person having latent syphilis (Strain 137). From one to three months after infection, no protective substances were found in the serum. Spirocheticidal substances were found after five months.

TABLE 7.—RESULTS IN EXPERIMENT 7

Serum	Test Strain of S. pallida	Days Positive for S. pallida	Days Negative When Bled	Days Since Infection	Result
(I)137*	137	26	69	144	Protection; animals well
(II)137	137	21	40	98	Positive lesions, 42-45 days
(II)137	(Control)				Negative; animals well
(III)137	137	14	28	67	Positive lesions after 38 to 42 days
(III)137	(Control)				Negative; animals remained well
(IV)137	137	9	10	40	Positive lesions after 42 to 45 days
(IV)137	(Control)				Negative; animals remained well
Normal rabbit	137				Positive lesions after 38 to 44 days

*In all of these protocols, the Roman numeral enclosed in brackets refers to the generation of the given strain of Spirochaeta pallida which was employed for experimental inoculation.

Experiment 8.—A series of rabbits was inoculated with Strain 117 which was isolated from the semen of a case of latent syphilis. The serums from a number of these animals were tested against a heterologous strain, No. 169. Protective substances were found in serums from six to fourteen months after infection, for homologous and heterologous *Spirochaeta pallida.*

TABLE 8.—RESULTS IN EXPERIMENT 8

Serum	Test Strain of S. pallida	Days Positive for S. pallida	Days Negative When Bled	Days Since Infection	Result
(II)117	117	91	117	402	Protection; animals remained well
(III)117	117	Spirochetes could not be found in dark-field examinations		270	Protection; animals remained well
(III)117	117, 169	25	146	197	Protection; animals remained well
(III)117	117	18	156	197	Protection; animals remained well
(IV)117	117, 169	12	123	160	Protection; animals remained well
Normal rabbit	117				Positive lesions after 28 to 34 days

The next experiment shows in a more definite manner the difference between serums from animals in a state of infection approximating latency and those that have not yet reached that condition. There is, moreover, a distinct difference

seen in the outcome of the test when a heterologous strain of spirochetes is used, thus contrasting with the serums from rabbits which had been inoculated with latent strains.

TABLE 9.—RESULTS IN EXPERIMENT 9

Serum	Test Strain of S. pallida	Days Positive for S. pallida	Days Negative When Bled	Days Since Infection	Result
(I)170	170	42	61	143	Positive lesions after 20 to 25 days
(I)170	(Control)				Negative; animals remained well
(I)170	170	42	138	220	Protection; animals remained well
(II)170	170	7	36	77	Positive lesions after 34 days
(II)170	(Control)				Negative; animals remained well
(III)170	170	15	47	92	Positive lesions, 50 days
(III)170	170	15	200	245	Protection; animals well
(III)170	169	15	200	245	Positive lesions; 36 days
(IV)170	170	13	0	33	Positive lesions after 27 days;
(IV)170	(Control)				Negative; animals remained well
(IV)170	170	13	166	199	Protection; animals remained well
(IV)170	169	42	109	171	Positive lesions after 36 days
(VIII)170	170	6	198	276	Protection; animals remained well
(X)170	170	24	121	172	Protection; animals remained well
(VI)169	169	24	152	199	Protection; animals remained well
Normal rabbit	169, 170				Positive lesions after 29 to 31 days

The conclusion which may be drawn from these results is that serums from rabbits experimentally infected with syphilis are uniformly negative for spirocheticidal properties except in those instances in which the infection has attained a relatively latent state which corresponds roughly to conditions in human syphilis.

DISCUSSION

The foregoing experiments have shown that latent syphilis in man is associated with a spirocheticidal property in the serum. This specificity is manifested at a time when the individual is outwardly free from the disease and appears to be well. When the infection is still active or is of recent origin, the protective element is not present in the serum. Substantially the same results are obtained with experimentally infected rabbits.

These observations would tend to confirm the belief that a true immunity does obtain at some time in the course of syphilic infection. A state of latency would imply a balance that has been struck between the antibodies in an infected person and the invading spirochetes. The presence of *Spirochaeta pallida* in latent syphilitic persons [9] is additional evidence in support of this idea. During that stage the spirochetes are innocuous for the host.

Immunity, in any sense, need not imply a condition which is incompatible with the life of a parasite. Resistance on the part of the host may be nicely balanced against that of the organism which continues to exist in certain surroundings without giving rise to manifestations characteristic of the disease. There are striking analogies in trypanosome infections, spirillary diseases and the carrier state in well-known diseases, such as typhoid and malaria.

The cyclic changes in syphilis are associated with reactions which point to a progressively increasing immunity on the part of the tissues. In the tertiary stage there is evidence of immunity in the paucity of *Spirochaeta pallida* in gummatous lesions and in the manifestations which conform to characteristic sensitization phenomena. A counterpart may be found also in tuberculosis and glanders. The mechanism by which immunity in syphilis develops would seem to be an elaboration of antibodies which is progressive and commences at the time when initial lesions are present. This begins as a local immunity reaction which extends from one group of tissues to another with a corresponding elaboration of specific substances into the blood. There is considerable evidence to support this view in some recent work [11] which has shown that a definite effect is exerted by one group of tissues on another in the production of clinical types of syphilis in the rabbit. The inhibitory effect of one local lesion on the development of lesions elsewhere has been mentioned by Nichols [7] and more recently by Brown and Pearce.[8]

Failure to reinoculate with syphilis has been taken to mean existing disease rather than a state of immunity. This view, which has gained credence through Neisser and his school, can be interpreted from a different angle by supplementing the older facts with newer ones. The presence of *Spirochaetae pallidae* in organs and tissues of the body appears to be coexistent with immunity to reinfection in exactly the same sense as this occurs in piroplasmoses and trypanosome diseases. The immunity in these infections persists as long as the parasites are present, and the serum in some degree is known to have protective antibodies. In a similar manner, the presence in the human or animal body of *Spirochaetae pallidae* possessing full virulence when inoculated into new soil need not signify disease, but rather a latent stage in which the spirochetes are able to survive in the immunized body. The reaction which takes place is a reversible one, and it is likely that failure to reinfect with syphilis means simply the entry of spirochetes into surroundings which favor lodgment of organisms without the setting up of visible lesions or manifestations of a definite kind.

The old conception of immunity in syphilis was based on meager if not erroneous knowledge as to the mechanism of infection, the

dissemination of the spirochetes, and what was meant by generalization of the disease. More recent experimental study along these lines (Eberson,[9] Brown and Pearce [10]) has given a different cast to immunity phenomena. Early dissemination of *Spirochaetae pallidae* makes possible an early absorption of antibodies, until with the lapse of sufficient time, these accumulated products are discharged into the blood stream from different parts of the body where the spirochetes may have lodged. The blood immunity, which appears to prevail when syphilis is unequivocally latent, is a progressive development of an extensive tissue immunity which has been produced gradually in the infected person.

SUMMARY AND CONCLUSIONS

The blood serum from persons having latent syphilis was found to have spirocheticidal properties. Rabbits were protected uniformly against infection with virulent *Spirochaeta pallida* in combination with such serums.

Protective properties were found in the serums of asymptomatic persons with latent syphilis with the following histories:

Infection with syphilis dating back from three to twenty-five years.

Patients who had received treatment until the Wassermann reaction had become negative.

A number of patients who had no history of infection, who had taken no treatment, and who had a slightly positive Wassermann reaction usually in the cholesterin antigen.

A group of patients in whom the Wassermann reaction was slightly positive in the cholesterin and noncholesterin antigens, or strongly positive in either one, in inverse relationship.

An infant whose mother's serum was found to contain spirocheticidal properties.

Spirocheticidal activity of serums in latent syphilis is of such a character as to prevent the normal dissemination of *Spirochaeta pallida* from a primary focus. Failure to inoculate rabbits with mixtures of serums and spirochetes was correlated with negative inoculations with the blood from such animals.

In the experimental animal, spirochetolytic serum may be developed in the course of six months to one year after the infection. In the rabbit, as in man, protective substances are found at a time when the infection has attained a relatively latent state.

The presence of these substances in given serums apparently depends on the stage of infection. When definite latency has been established, the serum appears to protect against experimental inoculation, whereas the serum from cases of early syphilis or those in which true latency has not been attained is not spirocheticidal.

Spirocheticidal activity is essentially a function of time and depends on the degree to which the individual has elaborated and distributed the slowly accumulating antibodies.

Serums which were developed in rabbits by strains of *Spirochaeta pallida* from latent sources manifested a wider range of protective properties, as shown by the inhibitory effect on heterologous as well as homologous strains. Serums from latent cases behaved similarly. Chancre strains when used for experimental infection were not capable of developing spirocheticidal serums for heterologous organisms, in the few experiments which were attempted.

A negative Wassermann reaction following antisyphilitic treatment may or may not go hand in hand with spirocheticidal activity of serums. Continued treatment which renders a Wassermann reaction negative does not appear to nullify any existing protective property of the given serum.

By analogy with trypanosome and spirillary diseases and the carrier state of certain well-known infections, syphilis offers immunity phenomena which tend to explain latency on the basis of a blood immunity which is developed progressively from tissue immunity.

The mechanism by which immunity in syphilis develops would seem to be an elaboration of antibodies commencing at the time when initial lesions are present and continuing as a progressive extension of local immunity from one group of tissues to another until the immune substances are absorbed by the blood stream. Latent *Spirochaeta pallida* thus become innocuous for the host.

The presence of *Spirochaeta pallida* at certain times in the human or animal body need not imply disease but rather a latent stage in which the spirochetes are able to survive in the immunized body. Failure to reinfect with syphilis means, from this point of view, the entry of spirochetes into surroundings which favor lodgment without setting up of visible lesions or manifestations. Immunity need not imply a condition which is incompatible with the life of a parasite. Latency, then, connotes a balance that has been struck in the individual between the antibodies and the invading parasites.

The results of the experiments reported in this paper suggest that the serum from definitely established latent cases of syphilis may prove of therapeutic value.[31]

---

31. In addition to the references given, the following may be of interest:
Bender: Deutsch. med. Wchnschr. **32**:1318, 1906.
Blaschko: Arch. f. Dermat. u. Syph. **105-106**:65, 1910-1911.
Brown, W. H., and Pearce, L.: J. Exper. M. **31**:729, 1920; **32**:473, 1920.
Hoffmann: Deutsch. med. Wchnschr. **34**:1546, 1911; Berl. klin. Wchnschr. 1905, No. 46; Centralbl. f. Bakteriol., Ref. Abt. 1 **38**:110, 1906; Dermat. Ztschr. **13**:561, 1906.

Landsteiner: Centralbl. f. Bakteriol., Ref. Abt. 1 **41**:785, 1908.
Landsteiner and Finger: Centralbl. f. Bakteriol., Ref. Abt. 1 **38**:107, 1906.
Levaditi: Ann. de l'inst. Pasteur **18**:129, 511, 1904; **20**:4, 1906.
Manteufel: Arb. d. k. Gsndhtsamte **27**:337, 355, 1908.
Uhlenhuth and Mulzer: Arb. d. k. Gsndhtsamte **44**:307, 1913.
Zinsser, Hans, and Hopkins, J. Gardner: The Viability of the Spirochaeta Pallida in Diffuse Light at Room Temperature, J. A. M. A. **62**:1802 (June 6) 1914; J. Exper. M. **21**:576, 1915.

REFRACTOMETRIC STUDIES IN HUMAN SYPHILIS WITH SPECIAL REFERENCE TO CHANGES DURING TREATMENT WITH ARSPHENAMIN AND NEO-ARSPHENAMIN*

KEIICHI TOKUDA, M.D.
PHILADELPHIA

INTRODUCTION

The refractometric studies with the proteins of the serum in syphilis reported in this article were undertaken at the suggestion of Prof. John A. Kolmer as primarily bearing on the nature of the serum changes in this disease in relation to immunologic phenomena and as possibly yielding additional information as to the mechanism of the "reactions" sometimes developing after the intravenous injection of solutions of arsphenamin and neo-arsphenamin.[1] Various hypotheses have been advanced in explanation of these "reactions," among which those based on the formation of precipitates in vivo have attracted considerable attention. Berman[2] believes that precipitates may be produced because of the presence of an excess of serum globulins in the plasma, and advocates a simple test for determining whether or not the serum of a patient produces precipitates with alkalinized solutions of arsphenamin in vitro.

Schamberg, Tokuda and Kolmer,[3] however, found that the test is without practical value and that the production of precipitates in vitro in this test is directly influenced by the amount of alkali present in the solutions of arsphenamin and neo-arsphenamin.

REVIEW OF LITERATURE

A number of investigators have found that when animals are immunized with bacteria, toxins and proteins, an increase in the serum globulins takes place.

---

* From the Dermatological Research Institute and the Wistar Institute of Anatomy, Philadelphia.

*Investigation aided by funds accruing from the preparation of arsphenamin.

1. Schamberg, J. F.; Kolmer, J. A.; Raiziss, G. W., and Weiss, C.: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **1**:235-255 (March) 1920.

2. Berman.: The Nitrotoid Crisis After Arsphenamin Injections, Arch. Int. Med., 1918. **22**:217-224, (Aug.) 1918.

3. Schamberg, J. F.; Tokuda, K., and Kolmer, J. A.: A Study of Arsphenamin Serum Precipitates and Their Relation to Clinical Reactions, Arch. Dermat. & Syph. **3**:263 (March) 1921.

Rowe [4] found that in all infections, except acute tonsillitis, typhoid fever and certain mild infections, the globulins were definitely increased. The globulins are also increased in syphilis. There is, however, no direct relation between the substance ("reagins" of "antibodies") which give rise to the Wassermann reaction and the increase of the globulins. Rowe reports that in syphilis the average value of globulins is definitely *increased* over the normal value, while that for nonprotein constituents is only very slightly increased. In a case in which the clinical diagnosis of the early lesion was chancre, the percentage of globulin was found to be normal, but in particularly severe cases of syphilis, the percentage of globulin was found to be the highest.

Winternitz [5] found that serum globulins were moderately increased in syphilis.

Elias, Neubauer, Porges and Salomon [6] thought the active substance causing the Wassermann reaction belonged to the globulins, and that they were present in greater amount in syphilis than in normal serum.

Noguchi [7] and other investigators also found that the globulins are increased in syphilis.

Hurwitz and Meyer [8] found that the progress of bacterial infections in experimental rabbits is usually associated with an *increase* of the globulin, provided the infection is severe; a mild chronic infection may continue for a long time without causing a marked change in the relation of the serum protein. Immunization with carefully controlled doses could be attained without a decided increase of globulins. Ordinarily when an animal reacts severely, the globulin is increased.

E. S. Schmidt and C. L. A. Schmidt [9] report that a decrease of serum proteins followed the injection of benzene (benzol), though no change occurred in the protein quotient.

Cervello [10] reports that after administering antipyrin to dogs, he finds an increase of both globulins and of total proteins.

---

4. Rowe, A. H.: Refractometric Studies of Serum Proteins in Nephritis, Cardiac Decompensation, Diabetes, Anemia, and Other Chronic Diseases, Arch. Int. Med., **19**:354-366, (March) 1917.

5. Winternitz, R.: Ein Beitrag zur chemischen Untersuchung des Blutes rezent leutischer Menschen, Arch. f. Dermat. u. Syph. **93**:65-72, 1908.

6. Elias, H.; Neubauer, E.; Porges, O., and Salomon, H.: Theoretisches über die Serumreaktion auf Syphilis, Wien. klin. Wchnschr. **21**:748-752, 1908.

7. Noguchi, H.: The Relation of Protein, Lipoid and Salts to the Wassermann Reaction, J. Exper. Med., **11**:84-99, 1909.

8. Hurwitz, S. H., and Meyer, K. F.: I. The Serum Globulin in Bacterial Infection and Immunity, J. Exper. Med. **24**:515-546 (Nov.) 1916.

9. Schmidt, E. S., and Schmidt, C. L. A.: On the Noninfluence of Injections Upon the Proteins of Globulin and Albumin in Blood Serum, J. Immunology, **2**:343 (June) 1917.

10. Cervello, C.: Einfluss der antipyretica auf die Albuminoide des Blutserums, Arch. f. exper. Path. u. Pharmakol. **10**, **62**:357-364, 1909.

Hurwitz and Whipple [11] found that the intoxication which develops after an acute or chronic obstruction of the intestine is in most instances associated with definite change in the blood proteins. In a simple obstruction with toxic death, the globulins may rise to double their initial value within forty-eight hours after the production of the obstruction. In the majority of such instances, the globulins continue high until death occurs. Similarly, animals with a chronic obstruction show a rise in the serum globulins. In these animals, the globulin increase takes place more slowly, but it may be of great magnitude and may show a tendency to return to its initial value.

Meyer, Hurwitz and Taussig [12] report that the percentage of serum globulins increases markedly during the course of immunization with diphtheria, tetanus, and botulinus toxin. In the case of botulinus toxin, however, there is first an initial rise in the albumin fraction.

These investigators found no constant relationship between the percentage increase in the serum globulin and the antitoxic potency of the serum. They conclude that the rise in globulins may be a manifestation of an upset in the delicate protein balance of the blood, resulting from the disturbed metabolism following the toxin inoculation.

Hurwitz and Meyer [13] report that the progress of an infection is usually associated with marked changes in the serum proteins. There may be an increase in the percentage of the total proteins during some stage of the infection; there is usually a change in the albumin-globulin ratio with an increase in the total globulins. The nonprotein constituents of the blood show fluctuations with a tendency to rise as the infection progresses. Seng [14] found increased globulin in serum from animals immune to diphtheria. Jakoby [15] found the euglobulins increased in animals immunized to castor oil. Moll [16] reports that in

---

11. Hurwitz, S. H., and Whipple, G. H.: Studies on the Blood Proteins. II. The Albumin-Globulin Ratio in Experimental Intoxication and Infections, J. Exper. Med., **25**:231-253 (Feb.) 1917.

12. Meyer, K. F.; Hurwitz, S. H., and Taussig, L.: Studies on the Blood Proteins. III. Albumin-Globulin Ratio in Antitoxic Immunity, J. Infect. Dis., **22**:1-27 (Jan.) 1918.

13. Hurwitz, S. H., and Meyer, K. F.: Studies on the Blood Proteins I. The Serum Globulins in Bacterial Infection and Immunity, J. Exper. Med., **24**: 515-545 (Nov.) 1916.

14. Seng, W.: Uber die qualitationen und quantitationen Verhältnisse der Eiweisskorper im Diptherieheilserum, Ztschr f Hyg. u. Infectionskrankh, **31**: 513-532, 1899.

15. Jakoby. M.: Uber Ricin-Immunitat, Beitr. z. chem. Phys. u. Path., **1**:51-77, 1901-1902.

16. Moll, L.: Uber künstliche Umwandlung von Albumin in Globulin, Beitr. z. chem. Phys. u. Path. **4**:563-577, 1903; Uber Blutveranderungen nach Eiweissinjektionen, ibid. **4**:578-589, 1903.

animals injected with various proteins, including gelatin and killed bacteria, a marked increase in the globulin content occurs, and he concludes that an increase in immune bodies is associated with an increase in the globulins. Langstein and Mayer [17] report that the serum proteins are increased in immunized and infected rabbits, the increase being largely in the globulin fraction.

SCOPE OF THIS INVESTIGATION

The subjects studied in this part of our investigation were:

1. A comparison of the values of the refractometric index of the serum and of the percentage of serum albumin and serum globulin in normal human serums (collected from the literature) with the values found in *untreated* human syphilis (author's observations) during the various stages of the disease.

2. A comparison of the changes in the blood serum of patients with syphilis in relation to the Wassermann reaction before treatment.

3. The changes in the refractometric index and in the percentage of serum proteins during the course of treatment with arsphenamin; patients classified according to their degree of resistance to antisyphilitic treatment.

4. The changes during treatment with neo-arsphenamin.

MATERIALS AND METHODS OF INVESTIGATION

All the determinations of the albumin, globulins and nonprotein constituents of the blood of syphilitic patients were made by the microrefractometric method of Robertson.[18] The Pulfrich refractometer was used and the percentages of the various constituents were calculated in all cases in the manner presented in detail by Robertson. The tests were made with sodium light.

All the arsphenamin and neo-arsphenamin used in these experiments was produced at the Dermatological Research Institute, Philadelphia. These drugs were injected intravenously in the treatment of syphilitic patients at intervals of from three to four or seven days by the following method:

Arsphenamin (dose from 0.4 to 0.6 gm.) was dissolved in distilled water (from 80 to 120 c.c.) and neutralized with a sufficient amount of sodium hydroxid to produce the disodium salt, as described by Schamberg, Kolmer, Raiziss and Weiss.[1] The injections were made

17. Langstein, L., and Mayer, M.: Uber das Verhalten der Eiweisskörper des Blutplasmas bei experimentellen Infektionen, Beitr. z. chem. Phys. u. Path. **5**:69-82, 1904.

18. Robertson, T. B.: A Microrefractometric Method of Determining the Percentages of Globulin and Albumin in Very Small Quantities of Blood Serum, J. Biol. Chem. **22**:233-239, 1916.

by means of a gravity apparatus. Neo-arsphenamin (dose 0.9 gm.) was injected in a volume of 10 c.c. of distilled water with the use of a Luer syringe. No extra alkali was added.

Blood was obtained from the median basilic vein in every case just before an injection. Two sterile test tubes were used for collecting the blood, the first, for the Wassermann reaction, and the second

TABLE 1.—Refractometric Determinations on Human Serums in Various Stages of Untreated Syphilis

Case	Sex*	Age	Clinical Diagnosis	Wassermann Reaction	Refractometric Index	Percentage of			Relative Amounts of	
						Total Proteins	Albumin	Globulin	Albumin	Globulin
15	♂	11	Congenital.....	++++	1.34924	5.71	5 38	0.33	94	6
14	♀	14	Congenital.....	++++	1.35036	6.64	5.83	0.81	88	12
16	♀	17	Congenital.....	++++	1.35010	6.06	4.54	1.52	74	26
R 1†	..	..	Primary.....	—	.....	7.60	6.40	1.20	84	16
4	♂	19	Secondary.....	++++	1.35036					
13	♂	20	Secondary.....	++++	1.35197	7.11	6.14	0.97	86	14
22	♂	21	Secondary.....	++++	1.35106	7.19	5.69	1.50	79	21
24	♂	21	Secondary.....	++++	1.35045	6.96	5.38	1.58	77	23
5	♂	24	Secondary.....	++++	1.35509					
11	♂	26	Secondary.....	++++	1.35236	7.51	5.19	2.32	69	31
8	♂	28	Secondary.....	++++	1.35132	7.28	5.66	1.62	78	22
2	♂	28	Secondary.....	++++	1.35045	7.28	5.90	1.38	81	19
27	♂	30	Secondary.....	++	1.35113					
12	♂	31	Secondary.....	++++	1.35097	6.97	5.49	1.48	79	21
10	♂	32	Secondary.....	++++	1.35053	6.66	5.53	1.13	83	17
31	♂	37	Secondary.....	++	1.35002	6.02	4.36	1.66	72	28
28	♂	38	Secondary.....	++	1.35088	7.01	5.62	1.39	80	20
9	♂	45	Secondary.....	++++	1.35071	6.34	4.46	1.88	70	30
3	♂	50	Secondary.....	++++	1.35036	6.70	4.85	1.85	72	28
25	♀	19	Secondary.....	++++	1.35810	10.12	5.61	4.51	55	45
32	♀	23	Secondary.....	++	1.35245					
30	♀	23	Secondary.....	++	1.35149					
18	♀	25	Secondary.....	++++	1.35123	6.96	5.62	1.32	81	19
19	♀	25	Secondary.....	++++	1.35036	6.70	5.62	1.08	84	16
23	♀	26	Secondary.....	++++	1.35342	7.97	6.26	1.71	78	22
21	♀	29	Secondary.....	++++	1.35002	6.53	5.39	1.14	82	18
33	♀	38	Secondary.....	++	1.35026	6.03	5.24	0.79	87	13
20	♀	40	Secondary.....	++++	1.35079	7.07	5.81	1.26	82	18
1	♀	41	Secondary.....	++++	1.35210	7.53	6.47	1.06	86	14
R 2	..	..	Early secondary	—	.....	7.60	5.30	2.30	70	30
R 3	..	..	Early secondary	+++	.....	7.90	4.60	3.30	58	42
R 4	..	..	Early secondary	+++	.....	7.40	5.40	2.00	73	27
R 5	..	..	Early secondary	+++	.....	8.30	6.10	2.20	73	27
R 8	..	..	Early secondary	+++	.....	7.30	3.70	3.60	51	49
R14	..	..	Secondary.....	+++	.....	8.10	5.20	2.90	64	36
R18	..	..	Late secondary..	+++	.....	7.30	5.40	1.90	74	26
R13	..	..	Tertiary.....	+++	.....	7.10	4.60	2.50	65	35
R15	..	..	Tertiary.....	+	.....	7.40	4.50	2.90	61	39
29	♂	50	Tertiary.....	++	1.34829	5.78	5.08	0.70	88	12
17	♂	70	Tertiary.....	++++	1.35045	6.77	5.06	1.71	75	25
7	♂	42	Tabes.....	++++	1.35105	7.20	5.79	1.41	80	20
6	♂	54	Tabes.....	++++	1.35184	7.58	5.91	1.67	78	22
G—	♂	20	.....	+	1.35090					
G—	♂	26	.....	+	1.35140					

* In this column and in the following tables, ♂ represents male, and ♀ female.
† R indicates cases taken from the paper of Rowe; G indicates cases taken from the paper of Gettler and Baker; all other cases are the author's.

for the refractometric investigations. We thus prevented traces of water or alcohol which might have remained in the needle from getting into the blood and vitiating the refractometric determinations. The specimens, in stoppered test tubes, were kept in the refrigerator over night, and were centrifugalized the next morning to obtain clear serum, which was studied.

The cases were patients with untreated syphilis from the clinic of Dr. Jay F. Schamberg, Polyclinic Hospital, Graduate School of Medicine, University of Pennsylvania, Philadelphia. The urine of each patient was regularly examined and injections were made only when no albumin was demonstrable.

THE REFRACTIVE INDEX AND PERCENTAGE OF SERUM PROTEINS IN SYPHILITIC BLOOD SERUM COMPARED WITH NORMAL SERUM

In order to aid in the interpretation of our results, we have collected from the literature all the available data on refractometric studies on human blood under normal conditions as well as in syphilis, and have compared these figures with our own observations on *untreated* syphilitic cases. A summary of these data is presented in Tables 1 and 2.

From the work of Rowe [19] we have the following data as to the range of the serum proteins in a series of twenty-two normal human cases: Albumin varies between 4.5 and 6.7 per cent., with an average value of 5.6 per cent.; globulin varies between 1.2 and 2.3 per cent., with an average value of 1.9 per cent; total proteins between 6.5 and 8.2 per cent., average value 7.5 per cent; relative amount of globulin 16 to 32 per cent., average value 25.5 per cent.

Gettler and Baker [20] in their refractometric studies on a series of twenty-eight *normal* cases give the limits of variation of the refractive index (ND) from 1.34900 to 1.35210, with an average value of 1.35045. (These figures have been obtained by converting their figures to the Robertson system by the addition of 1.33320—the refractive index of water. Any changes arising from this correction should be slight and should not affect the conclusions drawn from them.)

With these normal figures as a basis of comparison, we may now turn to the subject of syphilis. Our own values based on a series of thirty-two untreated cases may be summarized as follows: The refractometric index varies between 1.34829 and 1.35810, the average value being 1.35123. The percentage of total proteins varies between 5.78 and 10.12 per cent., the average being 6.95 per cent. Percentage of albumin ranges from 4.36 to 6.47 per cent., average 5.48 per cent.; globulin from 0.33 to 4.51 per cent., average 1.47 per cent.; relative amount of albumin from 55 to 94 per cent. of the total proteins, average value 79 per cent.; relative amount of globulin varies from 6 to 45 per cent. of the total proteins, the average being 21 per cent.

---

19. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med., **18**:455-473 (Oct.) 1916.

20. Gettler, A. O., and Baker, W: Chemical and Physical Analysis of Blood in Thirty Normal Cases, J. Biol. Chem. **25**:211-222 (June) 1916.

Rowe's results in syphilis (based upon ten untreated cases) are as follows: The total proteins varied between 7.1 and 8.3 per cent., the average being 7.6 per cent.; albumin varied between 3.7 and 6.4 per cent., average 5.12 per cent.; globulins between 1.2 and 3.6 per cent., average, 2.48 per cent.; relative amount of globulin varied between 16 and 49 per cent. of the total proteins, averaging 37.3 per cent.

Gettler and Baker in two cases with positive Wassermann reactions give the value for refractive index as 1.35090 and 1.35140.

It is evident, if we compare figures, that there is a marked increase in the refractometric index of the serum in syphilis, *especially in active*

TABLE 2.—SUMMARY OF REFRACTOMETRIC DETERMINATIONS IN UNTREATED HUMAN SYPHILIS: AVERAGE VALUES OF AUTHOR'S SERIES (THIRTY-TWO CASES)

	Refractometric Index	Percentage of			Relative Amounts of	
		Total Proteins	Albumin	Globulin	Albumin	Globulin
Average values of entire series	1.35123	6.95	5.48	1.47	79	21
Limits of variation from	1.34829	5.78	4.36	0.33	55	6
to	1.35810	10.12	6.47	4.51	94	45
Average of three congenital cases	1.34990	6.13	5.24	0.89	86	14
Average of twenty-five secondary cases	1.35152	7.44	5.87	1.57	79	21
Average of four tertiary cases	1.35041	6.83	5.46	1.37	80	20
Average and range of values of refractive index and serum proteins classified according to the Wassermann reactions of the serums						
Wassermann reaction ++++ (25 cases)	1.35126	7.00	5.55	1.45	79	21
Limits of variation from	1.34924	6.02	4.36	0.33	55	6
to	1.35810	10.12	6.47	4.51	94	45
Wassermann reaction ++ (7 cases)	1.35065	6.35	5.07	1.28	80	20
Limits of variation from	1.34829	5.78	4.36	0.70	72	12
to	1.35245	7.01	5.62	1.66	88	28
Average of values of Rowe's series (10 cases)						
Average	.....	7.60	5.12	2.48	68	32
Limits of variation from	.....	7.10	3.70	1.20	51	16
to	.....	8.30	6.40	3.60	84	49

secondary cases. The total proteins show a similar change, the increase being in globulins.

When we compare our values with those of Rowe for syphilis, we observe that the number of cases in our series being much greater, our range of total proteins is much wider, giving us a somewhat lower average. Our albumin average is somewhat higher. The variation in the globulins is much greater in our series and our average is much lower; the range of the relative amounts of globulin obtained by us is also much greater but our average is much lower.

If we classify our results according to the stages of syphilis, we see that the refractive index of the serum is highest in secondary cases, lowest in the congenital cases and is intermediate between these two in the tertiary cases. The figures for total proteins, albumins, globulins

and the relative amount of globulins are somewhat higher in secondary than in tertiary syphilis, the figures for congenital syphilis being somewhat lower than those of the latter.

If we compare these classified results with those of Rowe, we observe that our values of total proteins, albumin, globulin, and the relative amount of globulin in *tertiary syphilis* are lower. In secondary syphilis our values of total proteins, globulin, and the relative amount of globulin are lower.

Considering now the Wassermann reaction of the serum, we note that in the *strongly positive* cases, the values of total proteins, albumin, globulin, and the relative amount of globulin are higher than those in the *weakly positive cases.*

TABLE 3.—AVERAGES OF THE CHANGES IN THE ALBUMIN, GLOBULIN, AND TOTAL PROTEIN CONTENT OF THE BLOOD SERUM OF SYPHILITICS

	Refractometric Index	Percentage of			Relative Amounts of	
		Total Proteins	Albumin	Globulin	Albumin	Globulin
Series A. Cases yielding strongly positive Wassermann reactions						
Before injection	1.35126	7.00	5.55	1.45	79.3	20.7
After 1st injection	1.35096	6.97	5.54	1.43	79.5	20.5
After 2d injection	1.35059	6.70	5.40	1.30	80.6	19.4
After 3d injection	1.35065	6.69	5.43	1.26	81.2	18.8
After 4th injection	1.35073	6.97	5.60	1.37	80.3	19.7
After 5th injection	1.35078	6.93	5.59	1.34	80.7	19.3
After 6th injection	1.35061	6.83	5.53	1.30	81.0	19.0
After 7th injection	1.35053	6.83	5.54	1.29	81.1	18.9
After 8th injection	1.35049	6.86	5.50	1.36	80.2	19.8
Series B. Cases yielding weakly positive Wassermann reactions						
Before injection	1.35065	6.35	5.07	1.28	79.8	20.2
After 1st injection	1.35025	6.39	4.98	1.41	77.9	22.1
After 2d injection	1.34926	5.98	4.72	1.26	78.9	21.1
After 3d injection	1.35054	6.67	5.33	1.34	79.9	20.1
After 4th injection	1.35047	6.42	5.04	1.38	78.5	21.5
After 5th injection	1.34973	6.56	5.32	1.24	81.1	18.9
After 6th injection	1.34985	6.34	5.14	1.20	81.1	18.9
After 7th injection	1.35028	6.74	5.49	1.25	81.5	18.5
After 8th injection	1.35045	7.02	5.69	1.33	81.1	18.9

The weakly as well as the strongly positive cases in our series show values for total proteins, globulin, and the relative amounts of globulin lower than those of Rowe, the values for the albumin of the strongly positive series being somewhat higher. In the weakly positive cases, our values of albumin are lower.

THE CHANGES OCCURRING IN SYPHILIS DURING TREATMENT WITH ARSPHENAMIN AND NEO-ARSPHENAMIN

1. *A Comparison of the Changes in Refractive Index and Serum Proteins During Arsenical Treatment; Patients Classified According to the Wassermann Reaction of the Serums Before Treatment.*—As will be seen from Table 3, the curve of the refractive indexes of the

strongly positive serums shows a fairly progressive downward course throughout the period of treatment. The weakly positive serums, on the other hand, show very irregular fluctuations throughout treatment.

The percentage of total proteins shows little or no change during the course of treatment in the strongly positive cases and tends to increase somewhat irregularly in the weakly positive cases.

TABLE 4.—Averages of Refractometric Changes During Arsenical Treatment Classified According to Interval of Injections

	Refractometric Index	Percentage of			Relative Amounts of	
		Total Proteins	Albumin	Globulin	Albumin	Globulin
1. Arsphenamin, 7 day intervals						
Before injection	1.35081	6.82	5.19	1.63	76	24
After 1st injection	1.35007	6.70	5.02	1.68	75	25
After 2d injection	1.35006	6.35	4.87	1.48	76	24
After 3d injection	1.35055	6.54	5.11	1.43	78	22
After 4th injection	1.35018	6.69	5.25	1.44	78	22
After 5th injection	1.35045	6.86	5.43	1.43	79	21
After 6th injection	1.35041	6.87	5.51	1.36	80	20
After 7th injection	1.35011	6.54	5.38	1.16	82	18
After 8th injection	1.35011	6.62	5.26	1.36	80	20
2. Arsphenamin, 3 or 4 day intervals						
Before injection	1.35135	7.13	5.40	1.73	76	24
After 1st injection	1.35177	7.28	5.61	1.67	77	23
After 2d injection	1.35004	6.76	5.31	1.45	78	22
After 3d injection	1.35051	6.53	5.20	1.33	79	21
After 4th injection	1.35011	6.97	5.45	1.52	78	22
After 5th injection	1.35210	7.43	5.71	1.71	77	23
After 6th injection	1.35101	6.92	5.34	1.58	77	23
After 7th injection	1.35023	6.91	5.34	1.57	77	23
After 8th injection	1.35173	7.42	5.76	1.66	78	22
3. Neo-arsphenamin, 7 day intervals						
Before injection	1.35121	6.87	5.70	1.17	83	17
After 1st injection	1.35007	6.89	5.72	1.17	84	16
After 2d injection	1.35050	6.72	5.54	1.18	82	18
After 3d injection	1.35071	6.78	5.64	1.14	83	17
After 4th injection	1.35104	7.00	5.74	1.26	82	18
After 5th injection	1.35039	6.05	4.92	1.13	83	17
After 6th injection	1.35041	6.66	5.55	1.11	83	17
After 7th injection	1.35071	6.90	5.79	1.11	84	16
After 8th injection	1.35039	6.91	5.76	1.15	83	17
4. Neo-arsphenamin, 3 or 4 day intervals						
Before injection	1.35106	6.86	5.35	1.51	78	22
After 1st injection	1.35038	6.49	5.08	1.41	78	22
After 2d injection	1.34996	6.65	5.41	1.24	81	19
After 3d injection	1.35057	6.90	5.60	1.29	81	19
After 4th injection	1.35042	6.88	5.50	1.38	80	20
After 5th injection	1.35033	6.65	5.12	1.53	80	20
After 6th injection	1.35068	6.80	5.42	1.38	80	20
After 7th injection	1.35077	6.86	5.48	1.48	79	21
After 8th injection	1.34999	6.64	5.33	1.31	80	20

The percentage of albumins shows an initial tendency to decrease in the strongly positive cases and gradually increase in the weakly positive. The globulins in the weakly positive series show an increase with the first injection and then fluctuate. In the strongly positive series, the globulins continue to decline very slowly but rather irregularly.

The relative amounts of the globulins show only a slight tendency to decline in the strongly positive; in the weakly positive series there is practically no change until after the fourth injection; then follows

a fairly progressive decline. The relative amounts of albumin tend to increase more uniformly in the strongly positive than in the weakly positive series.

2. The Changes in the Refractive Indexes and Serum Proteins of Syphilis Serums of Patients Treated With Arsphenamin and Neo-Arsphenamin, Classified According to the Interval of Injections.—(A) Weekly Intervals: The refractive index of the serum, when treatment with arsphenamin was given at seven day intervals, showed a marked drop after the first two injections then a rise and finally a gradual decline (Table 4.)

The refractive index when neo-arsphenamin was used shows a somewhat similar curve.

TABLE 5.—AVERAGE RESULTS OF TYPE I SERUMS *

	Refractometric Index	Percentage of			Relative Amounts of	
		Total Proteins	Albumin	Globulin	Albumin	Globulin
Type I serums						
Before injection	1.35089	6.97	5.41	1.57	77.6	22.4
After 1st injection	1.35144	7.12	5.51	1.61	77.4	22.6
After 2d injection	1.35048	6.72	5.32	1.40	79.2	20 8
After 3d injection	1.35067	6.63	5.25	1.38	79.2	20 8
After 4th injection	1.35064	6.96	5.45	1.50	78 3	21.7
After 5th injection	1.35076	6.90	5.48	1.41	79.4	20.6
After 6th injection	1.35082	6.85	5.43	1.43	79.3	20.7
After 7th injection	1.35063	6.88	5.41	1.49	78.6	21.4
After 8th injection	1.35088	6.99	5.52	1.52	79 0	21.0
Type II serums						
Before injection	1.35074	6.64	5.19	1.45	76.7	23.3
After 1st injection	1.35040	6.48	5.02	1.47	77.5	22.5
After 2d injection	1.35016	6.41	5.00	1.41	78.0	22.0
After 3d injection	1.35067	6.76	5.40	1.38	79.9	20.1
After 4th injection	1.35080	6.50	5.41	1.37	83.2	16.8
After 5th injection	1.35096	6.95	5.48	1.45	78.8	21.2
After 6th injection	1.35070	6.85	5.43	1.43	79.3	20.7
After 7th injection	1.35060	6.76	5.49	1.27	81.2	18.8
After 8th injection	1.35051	6.88	5.45	1.44	79.2	20.8

* Type I Serums: Cases strongly resisting antisyphilitic treatment. Type II Serums: Cases yielding readily to antisyphilitic treatment.

The percentages of total proteins and albumins under either arsphenamin or neo-arsphenamin treatment show curves which have something in common. There is a general tendency for the curves to fall after the first two injections; this is followed by a gradual rise above normal level about the fifth week, and after this rise the curves fluctuate.

The relative amounts of globulin show more rapid decline during weekly arsphenamin than neo-arsphenamin injections.

(*b*) Semiweekly Intervals: The series which was treated with arsphenamin at three or four day intervals shows curves somewhat different from the foregoing. The refractive index of the serum increases

slightly after the first injection, decreases rapidly after the second injection, and then the curve rises and falls irregularly.

In the cases which were treated with neo-arsphenamin, the refractive index drops fairly continuously after the first and second injection, rises slightly at the third injection and then remains practically unchanged.

The percentage of total proteins and albumins fluctuated after injection of either arsphenamin or neo-arsphenamin.

The relative amounts of globulin show about the same tendency to decline under neo-arsphenamin as under asphenamin treatment.

3. *A Comparison of the Refractometric Changes in Syphilitic Serums During Arsenical Therapy; Cases Classified According to Their Degree of Resistance to Antisyphilitic Treatment.*—The syphilitic cases are classified in this discussion into two types according to the degree of resistance during the course of treatment. To the first type belong the cases which resisted the treatment strongly; that is,

TABLE 6.—Summary of Data of the Author's Entire Series of Thirty-Two Cases, Showing the Averages of the Changes of the Refractive Index and Proteins of the Serum During the Course of Arsenical Treatment

	Refractometric Index	Percentage of			Relative Amounts of	
		Total Proteins	Albumin	Globulin	Albumin	Globulin
Before injection	1.35123	6.95	5.48	1.47	79	21
After 1st injection	1.35081	6.88	5.44	1.44	79	21
After 2d injection	1.35027	6.57	5.28	1.29	80	20
After 3d injection	1.35063	6.78	5.41	1.27	80	20
After 4th injection	1.35068	6.88	5.51	1.37	80	20
After 5th injection	1.35066	6.90	5.57	1.33	81	19
After 6th injection	1.35054	6.78	5.49	1.29	81	19
After 7th injection	1.35050	6.81	5.53	1.28	81	19
After 8th injection	1.35049	6.81	5.53	1.28	81	19

the Wassermann reaction was persistently positive; and to the second type belong the cases in which the Wassermann reaction became negative very readily.

(*a*) *Refractive Index of Serum.*—In the first type the refractive index of the serum shows little or no tendency to drop below its original value. On the contrary, we note an increased value with the first injection.

In the third type, there is a decided fall after the first two injections, followed by high levels up to the sixth week and ending in a decline of the curve.

(*b*) *Total Proteins*: The changes in the percentage of total proteins are almost parallel to those of the refractive index in each of the two types.

(*c*) *Relative Amounts of Globulins.*—The relative amounts of globulin in the first type show only a very slight tendency to decrease during the course of treatment.

In the second type there is more tendency for the curve to fall during the course of treatment.

4. *General Survey of the Average Refractometric Changes in Syphilis During Arsenical Treatment.*—If we consider the averages of the refractometric changes during arsenical treatment of our entire series of thirty-two syphilitic cases, without special classification, we note the following (Table 6):

(*a*) The refractive index and percentage of total proteins of the serum show a tendency to decrease more or less regularly during a course of injections of arsphenamin or of neo-arsphenamin.

(*b*) The albumin content of the serum shows irregular fluctuations.

(*c*) The relative amounts of globulins diminish fairly progressively.

COMMENT

It is generally conceded that the disturbances in metabolism incident to infection by various micro-organisms, including *Spirochaeta pallida,* are manifested in part by an increase in the viscosity of the blood and therefore of the refractive index, the percentage and relative amounts of the various serum proteins. In syphilis, and perhaps also in other infections, it may be assumed that these increases are really due in part or entirely to an augmentation in the lipins (cholesterol, lecithin, etc.) which are bound in a strong chemical union with the serum proteins. This phenomenon is no doubt a manifestation of the response of the body to invasion and injury, in other words, it is a phase of the inflammatory process.

As for the possibility suggested by Berman [2] that an increase in the serum proteins bring about their precipitation by arsphenamin in vivo, we have not found any correlation in our studies between clinical reactions and refractometric changes. The severe reactions after arsphenamin injections are in our opinion due either to technical errors in administration or to the presence of certain unavoidable and unrecognizable impurities in the drugs. This has been fully discussed by Schamberg, Kolmer, Raiziss and Weiss.[1]

The serum proteins, functioning as they do primarily in controlling the viscosity of the blood and to only a minor degree in controlling its hydrogen-ion concentration, probably only serve an insignificant rôle in the syndrome known as the "nitrodoid reaction." We shall have to search for more injurious disturbances, such as the action of

arsphenamin on the suprarenals or those due to general tissue destruction or kidney injury, to explain the mechanism of the severe reactions often observed after intravenous injections of arsphenamin and neo-arsphenamin.

SUMMARY

The general conclusion drawn from a review of the recent literature on refractometric studies in syphilis and other infectious diseases seems to be that increases in the globulins of the serum accompany severe infections or acute intoxications.

Refractometric studies were made upon thirty-two cases of untreated syphilis and the following observations were made:

1. There is a marked increase in the refractive index of the serum and also in the globulins in syphilis, especially in active secondary cases. This confirms the findings of Rowe.

2. The refractive index of the serum is highest in secondary cases, lowest in the congenital and is intermediate between these two in the tertiary cases. The figures for total proteins, albumins, globulins and the relative amount of globulin are somewhat higher in secondary than in tertiary syphilis, the figures for congenital syphilis being somewhat lower than those of the latter.

3. Considered in relation to the Wassermann reaction of the serums, before treatment, the strongly positive cases show values of total proteins, albumins, globulins and relative amount of globulins higher than the weakly positive cases.

4. During a course of eight intravenous injections of arsphenamin (0.4 to 0.6 gm.) and neo-arsphenamin (0.9 gm.), each drug being given at weekly and semiweekly intervals, the refractometric studies (made before each injection) show these results:

5. Classified according to the Wassermann reaction of the serums before treatment, there are no sufficiently constant or striking differences to warrant differentiating between the strongly and weakly positive series.

6. Considered according to the intervals of injection, the relative amounts of globulins show more *rapid* decline during weekly arsphenamin than neo-arsphenamin injections.

During semiweekly periods of administration the changes are about the same.

7. Classified according to the degree of resistance of the patients to antisyphilitic treatment (as indicated by repeated Wassermann tests) it was observed that: When the Wassermann reaction remained per-

sistently positive, the refractive index, the percentage of total proteins and the relative amount of globulins of the serum showed little or no tendency to drop below their original values. When the Wassermann reaction, on the other hand, became very readily negative, the curves fell, with more or less regularity during the course of injections.

STREPTOCOCCIC DERMATOSES *

ERNEST DWIGHT CHIPMAN, M.D.

SAN FRANCISCO

In the production of numerous dermatoses the streptococcus plays either a preponderant or an accessory rôle. In the one case, lesions result from the direct inoculation of the sound skin, giving rise to what may be considered a pure streptococcic dermatosis. In the other case, various complexes follow the inoculation of an antecedent affection, with the streptococcus either alone or in association with another organism.

As to what reactions may be properly classified as streptococcic in the strict sense, there is probably some divergence of opinion. Of course the simple occurrence of the organism in a lesion does not entitle it to be labeled one of the pure streptococcic dermatoses. To be fairly included in such a category, definite etiologic relationship must be established.

On the other hand, the presence of the streptococcus in a given case, even as an accessory, may be of greater practical importance than the question of its precise place in the nomenclature

For this reason, and for the purposes of this paper, no special stress will be placed on the question as to whether the streptococcus plays a dominant or a contributory part in the production of a given lesion.

The chief concern at this time is to consider not so much whether certain dermatoses are or are not of purely streptococcic origin as to review the reactions which seem to assume special characters because of the presence of the streptococcus.

At the outset Sabouraud's criteria of the presence of streptococci may be quoted: "Whenever an extensive area of skin oozes abundantly with a rosy, serous, limpid fluid; whenever one observes upon an eroded epidermal surface the presence of yellowish, unctuous, elevated or flat, but generally thin, papyraceous crusts, checkered with fissures, the presence of the streptococcus in the underlying lesion may be affirmed."

IMPETIGO CONTAGIOSA

The arch type of pure streptococcic dermatosis is impetigo contagiosa. The characteristic behavior of the skin invaded by streptococci may best be seen in this disease. While staphylococcic lesions tend to circumscription, streptococcic lesions tend to peripheral extension.

---

* Read before the Section on Dermatology and Syphilology at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

The exudate of streptococcic lesions is serous rather than purulent. The fibrinous exudate, which becomes apparent when the discharge diminishes, is also distinctive. It is thin, clear and whitish, or of a light, rosy hue.

The primary lesion of impetigo is a minute vesicle containing a clear, serous fluid. The corneous envelop is fragile and ruptures spontaneously or following slight trauma. An abundant effusion is at once in evidence and this quickly coagulates, forming the typical, yellowish crust. Beneath this crust the process continues; the surrounding corneous layer is elevated about the circumference, finally rupturing, whereupon a new and larger crust results.

While the streptococcus often evinces a selective preference for certain sites, such as the folds of the skin, this tendency is not noted in impetigo.

Just as impetigo may be regarded as a pure streptococcus infection of the epidermis so erysipelas may be considered with respect to the deeper tissues. The ordinary whitlow is generally considered as streptococcic in origin. Both of these conditions are on the borderline between surgery and dermatology.

A consideration of the purely dermatologic lesions in which the streptococcus plays a variable part is not only of interest but of importance from the standpoint of therapy. If we follow the French authors who have studied the question so minutely we shall deal with such topics as impetiginization, the distinction between impetigo, impetiginization and simple streptococcic infection, recurrent dermatoses from slumbering foci, the intertrigo group and various other consecutive reactions.

While many of these discussions may appear to be of only academic interest, their pursuit will tend rather to clarify than to confuse. A comparison of French and American textbooks leads inevitably to the conclusion that either French writers exaggerate or we minimize the importance of the subject.

IMPETIGINIZATION

One of the first questions to concern us is the application of the term impetiginization. As usually employed, this designates the characteristic symptoms of impetigo superimposed, no longer in isolated spots but diffusely, upon some preexistent dermatosis which, beneath the complication, retains its own individuality.

The essential difference between impetigo and impetiginization is that the former spreads by isolated foci while the latter spreads peripherally. When inoculated on an epidermis already open and deprived of its stratum corneum it can no longer form the characteristic vesicle, since the covering for it is wanting.

Some years ago the diagnosis of impetiginous eczema was frequently made. The picture conveyed by that term was roughly that of a crusted eczema. It retained a semblance of eczema but yielded to the treatment of impetigo.

Sabouraud has described and sought to make a definite entity of chronic streptococcic epidermitis. It occurs in three phases, the first of exudation, the second of prelichenoid impetiginization and the third of purely lichenoid aspect. In the end it presents dry, thickened patches covered with slightly scaly papules. At times it reverts to its exudative phase.

Darier considers this a chronic, microbic, lichenoid eczema. Neither Darier nor Brocq denies the presence of the streptococcus. The patches represent an appearance somewhat between that of chronic eczema and lichenification. Because they do not exhibit the pseudopapules of lichenification and because they show moisture at times, they are most often regarded as eczema, or eczema plus a microbic infection.

The question of infectious eczematoid dermatitis must be considered in this connection. Engman, who first described it, regards it as of staphylococcic origin but apparently includes in its category the condition formerly termed impetiginous eczema. Fordyce also includes under the same title many sharply defined dermatoses as well as lesions following ecthyma and intertrigo, all of which carry at least the suggestion of the streptococcus.

If the term is used in the comprehensive sense indicated by both of these writers it would seem to be descriptive of a group or better, perhaps, of a reaction rather than of a distinct entity. Moreover the cases recorded by each seem always to have been infectious at the outset and eczematoid only secondarily. This at once suggests the distinction that an infectious eczematoid dermatitis is an infection which has become eczematized, while an impetiginous eczema is an eczema which has become impetiginized.

I do not insist that the old impetiginous eczema was always primarily an eczema, but I do believe it incontestable that eczema often becomes secondarily infected with streptococci and that such cases present definite characters which are well described by the term impetiginization.

The case history presented herewith will be of interest:

REPORT OF CASE

L. D., a boy, aged 16 years, was vaccinated on the left arm six months ago. Infection supervened and healing was delayed. Crusted lesions developed about the wound, and subsequently another eruption appeared on the right thigh just above the knee. At the date of consultation both lesions were of several months' duration. The patch on the arm was obviously formed by the coalescence of a number of circular lesions. The surface was covered with a fine, fibrinous

exudate, with here and there a few crusts. It was apparently a frank case of impetigo. On the thigh was a circular area approximately 5 cm. in diameter, sharp in outline, markedly thickened and presenting some thin scales with a few exceedingly fine vesicles at the periphery. Aside from this last evidence the lesion was dry. The appearance was that of chronic streptococcic epidermitis of Sabouraud.

COMMENT

We find, then, in the same subject an uncomplicated impetigo and an infectious eczematoid dermatitis. Engman states that it is not unusual to find both conditions in the same person. If one grants the streptococcic origin of impetigo, it is difficult to eliminate the possibility of its influence in the consecutive eczematoid dermatitis.

It is true also that the form of infectious dermatitis so often observed following discharge from the nose, ears, sinuses, etc., in which the staphylococcus is the offending organism, may become eczematized.

From the evidence at hand it would seem difficult to consider infectious eczematoid dermatitis otherwise than in the light of an infection, either staphylococcic or streptococcic, eczematized. Furthermore, it would appear necessary to distinguish between it and an eczema, a dermatitis or any dermatosis which has secondarily become impetiginized. The distinction should rest on the character of the original eruption.

INTERTRIGO GROUP

Under the title "Chronic Sequelae of Acute Impetigo," Sabouraud has described a group of dermatoses which recur from time to time as the result of the activation of quiescent foci of streptococcic infection. This phase of the subject is intimately connected with the question of the intertrigo group.

Concerning intertrigo in general it may be noted that the marked predilection of the streptococcus for cutaneous folds is undeniable. Sabouraud maintains that all intertrigos are either primarily streptococcic or secondarily infected with the streptococcus. Often an intertrigo appears eczematous because of the fine vesicles it exhibits. These vesicles, however, are found at the periphery of the lesion. At the bottom of the fold will be found a fissure covered with the characteristic exudate and all such lesions will give within twelve hours a culture of streptococci.

The recurrent forms originate frequently in the retro-auricular fold. Behind the ear a yellowish, crusted lesion is observed. In pulling the ear forward to obtain a good view a fissure is opened. Two eroded surfaces are in apposition and their borders are covered with yellowish crusts. On removal of these crusts the underlying surface is seen to be covered with a fine, fibrinous exudate.

From such a chronic focus a process may extend directly, to involve considerable areas of the scalp, or the infection may be spread by the fingers, as in scratching. Until this more or less quiescent lesion is recognized and treated, recurrent attacks of impetigo may be the rule. The retro-auricular fold and the nostril are the two regions particularly prone to harbor these foci. Blepharitis is possibly of a like nature.

The term ecthyma has gradually come to mean an impetigo which, because of bad hygiene or anything lowering the resistance of the subject, has invaded the deeper tissues and caused rupia-like lesions which heal only with scar formation. Aside from their depth and indolence, they are not materially different from ordinary impetigo.

Likewise to be classified with chronic impetigo are the circumscribed forms of pityriasis simplex of the face, called by French authors "dartres volantes." These are seen chiefly in children, and in former times were regarded as evidence of a strumous diathesis. The lesions are circular or oval, superficial, well defined and covered with fine branny scales. While undoubtedly the streptococcus is the exciting cause, it is possible that the question of the soil is also to be carefully considered.

Another example of the preference of the streptococcus for the folds of the skin is perlèche. This infection attacks the labial commissures. The primary lesion is a fissure at the bottom of the fold which is somewhat eroded and on which the characteristic, fine, fibrinous exudate is seen. On each side of the fissure there is epidermal thickening. Cultures will give streptococci in a few hours.

SUMMARY

Each of the conditions we have discussed as streptococcic dermatoses presents a definite clinical picture.

Impetigo, ecthyma, intertrigo and perlèche are matters of such common agreement that no comment is needed.

Impetiginization is a diffuse form of impetigo secondarily affecting an antecedent dermatosis which retains its own individuality.

Infectious eczematoid dermatitis denotes the eczematization of an infection, the infection preserving its own character in spite of the complication.

Chronic forms of impetigo are frequent. They present such lesions as circumscribed plaques of pityriasis, as well as impetiginous processes behind the ears, on the scalp and about the nose and eyes.

The character of the soil and certain internal influences may account for some objective differences in lesions due primarily to streptococci.

What seems probably the determining factor of most importance is the variation in the organism itself.

Unna has maintained that different strains of streptococci may one day be demonstrated in the production of the various forms of impetigo. Certainly it will not appear far fetched to reason that, just as different strains of streptococci have been isolated in scarlatina, erysipelas and measles, so they may be isolated in impetigo, ecthyma, intertrigo and other dermatoses.

391 Sutter Street.

ABSTRACT OF DISCUSSION

Dr. August Ravogli, Cincinnati: I cannot agree with Dr. Chipman as to eczematoid dermatitis. Eczema is a dermatitis. Dermatitis is not an eczema, consequently the blending of the term "eczematoid dermatitis" is not very clear to me. That the streptococcus is the cause of a great many infections of the skin there is no doubt, as, for instance, the impetigo seen so often in children. Another disease caused by the streptococcus which Dr. Chipman did not mention is panaritium superficiale bullosum tourniole of Sabouraud, an infectious inflammation of the epidermis. It is a kind of bulla formation around the third phalanx of the finger and around the nail, containing purulent serum. I have seen a child infected with the streptococcus and in consequence thereof develop a dermatitis exfoliativa, the whole body being covered with the bullae. The nurses often develop a streptococcic infection from attending these patients. The question between eczema and kindred affections consists in the quality of the pus cocci. If it is staphylococcus or streptococcus, if the coccus is yellow, or of the Bockart variety that produces sycosis, all are capable of producing practically the same affection, only in different degree. The streptococcus in the skin is capable of producing some general affection and reaction in the system. The trichophyton fungus which vegetates superficially on the epidermis is capable of producing a general reaction and antibodies are formed. The streptococcus is capable of producing a lymphangitis and affecting the lymph vessels and causing cutaneous abscess.

Dr. Charles J. White, Boston: As to the differential diagnosis between the epidermophyton and streptococcic infections, it is often difficult to determine which disease is present. Those who have not worked with the epidermophyton may think it is simple to make cultures and demonstrate the plant, but such an idea is far from the truth. As Dr. Chipman has said, the streptococcic infections seem to spread peripherally. That is not what the epidermophyton does. It comes up as a vesicle and remains in that form. Another point is that the streptococcic lesions are larger than those produced by the epidermophyton.

Dr. Douglass W. Montgomery, San Francisco: Much of the advancement of our knowledge is due to French observers, particularly to Gougerot, who while at the front became acquainted not alone with streptococcic infections of the skin, but also with them as a disease of wounds. The Rockefeller Institute has also done much in differentiating the different strains of streptococci. The streptococci have several broad, general characteristics; one of them is their fondness for moisture. They like to dwell in moist places such as the folds of the skin, and, having infected the skin, they attract a vast quantity of serum to the infected area. It is now well known that the ordinary ulcer of the leg is a

streptococcic infection, and it is probable that the reason for the continuance of the infection in this situation is the unusual moisture of the tissues, due to venous stasis. Another broad characteristic of the streptococcus, determining its clinical behavior, is its anaerobic nature. A man will receive a wound, for instance, which becomes streptococcically infected, and the wound will heal. But it heals with colonies of viable streptococci inclosed in the tissue. Afterward, as so often happened in the war, a secondary operation for relief of a deformity is performed, which may be done with faultless aseptic technic. Nevertheless, a streptococcic infection takes place, emanating, not from the outside, but from the streptococci still resident in the tissues.

Dr. Frank C. Knowles, Philadelphia: While serving with the British forces in France I had an opportunity of seeing many forms of impetigo. McCormick, a well-known British dermatologist, who was at the front over four years carrying out a series of experiments to determine the nature of the offending streptococcus, found *Streptococcus faecalis* to be responsible in most cases. On returning home it occurred to me that a further study might prove interesting. Thirty cases were studied and of these twenty-eight were of the hemolytic strain. Unfortunately, five strains were discovered, but only one of the *S. faecalis* type.

Dr. Charles M. Williams, New York: The streptococci tend to form groups, surrounded by normal skin, whereas the ringworm infections are apt to be scattered here and there, not forming such distinct outlines. The second point is the frequent occurrence of such forms of pyodermia with infections of the nose. It is a common concomitant of catarrh. Frequently a report will come from the nose specialist stating that it is a simple rhinitis and does not amount to anything, but until you get some competent rhinologist to cure the rhinitis no treatment of the skin will result in cure.

Dr. Richard L. Sutton, Kansas City, Mo.: I believe that the staphylococcus is probably the most frequent cause of the disease as seen in this country, particularly in the Middle West. The streptococcus may be a secondary invader, or, as in the cases reported by Dr. Chipman and by Dr. Knowles and his associates, it may be the sole invader in some instances. In the cases of infectious eczematoid dermatitis studied by Engman, by Fordyce and by myself, *Staphylococcus aureus* was also the offending agent. A thought suggested by Dr. White is important: In many instances tinea infection may simulate other disorders, dermatitis repens, for example. It is an easy matter to recover the ubiquitous staphylococcus, but isolation of the ringworm fungus is often a difficult process; consequently, it may be that we blame the staphylococcus for many lesions that should be credited to its yeastlike cousin. Some years ago Dr. Howard Morrow called attention to the fact that silver nitrate was almost a specific in the treatment of impetigo, and I wish to commend it very highly to you. It is employed in aqueous solution, 10 per cent., and if the patient does not object to the discoloration, it is one of the most valuable agents in the treatment of this condition.

Dr. Ernest Dwight Chipman, San Francisco: I anticipated opposition to the views expressed concerning infectious eczematoid dermatitis. Dr. Sutton has defended the staphylococcus. There seems room for an honest difference of opinion on this score which time will probably settle to the satisfaction of all. Dr. Ravogli mentions the omission of the French tourniole from my list. I believe the term whitlow, which I touched on lightly, is the equivalent. Dr.

White properly emphasized the resemblance between some streptococcic lesions and the reactions due to the epidermophyton. In Dr. Engman's article, published nearly twenty years ago, on the subject of infectious eczematoid conditions, there appeared an illustration and description of a case which I believe he and all of us would unhesitatingly diagnose today as epidermophyton infection. It is probable that in the future we shall have a very much more specialized knowledge of the different strains of the streptococcus, not only those involving the deeper tissues but those which confine their activities more strictly to the epidermis.

Abstracts from Current Literature

THE PREVENTION OF SKIN TROUBLES FROM CUTTING OILS AND EMULSIONS. Report of the National Safety Council, Chicago, No. 44, 1921.

Workers in cutting oils and emulsions frequently develop, on the exposed parts, black follicular plugs which often become secondarily infected, or vesicular eruptions or vegetating tumors. Persons with excessively hairy or dry skins are predisposed.

Most oils as received from the manufacturer are sterile; those made from crudes containing little or no paraffin and which have been highly refined are the most favorable. Excessive amounts of hydrocarbon sulphonates and fatty acids are undesirable. Used, unfiltered oils containing bacteria from workers' sputums and hands, and metal chips are particularly irritating.

Prophylaxis is obtainable in most cases by rigid hygienic practices. The parts should be scrubbed thoroughly at least twice daily in hot running water with liquid or powdered soap and a soft brush. If oil or a mixture of green soap and sawdust is used for cleansing, each workman should have an individual supply. The application of hydrous wool fat (lanolin) after washing will prevent chapping. Cleanliness of clothing and machinery, gloves, oil-cloth armlets, and the prompt and proper treatment of small cuts will impede the development of many infections.

It is useless to try to prevent skin troubles among some men who show extreme susceptibility to the irritating action of cutting oils. Such men should be transferred to other work where they will not be brought into contact with such oils.

Intracutaneous sensitization tests with oils during the course of the disease have not proved of much practical value, as negative results are frequent and immunization is not feasible. Injections of nonspecific proteins do not seem to immunize. In infected cases, autogenous and stock vaccines are of slight value. Fractional doses of roentgen rays are frequently very helpful. When the eruption is a dermatitis venenata, the itching is greatly relieved by one or two fractional doses, and when the eruption is a pustular folliculitis, a furunculosis or an infectious eczematoid dermatitis, involution often results after a few fractional doses at weekly intervals, accompanied by wet dressings of Burows' solution and vaccines. Ultraviolet rays from the Kromayer or Alpine lamps are also effective. In mild infections calamine lotion is soothing. Stimulating or irritating local remedies or ultraviolet rays are not permissible during roentgen-ray treatment, as they greatly enhance the action of the roentgen rays and may lead to severe local reactions.

(The following references may be of interest:

White, R. P.: Occupational Affections of the Skin, New York, P. B. Hoeber, 1920, p. 144.

Shie, M. D.: Wound Infection Among Lathe Workers, J. A. M. A. **69**: 1927, 1917.)

Andrews, New York.

DRACONTIASIS IN ANIMALS: WITH NOTES ON A CASE OF GUINEA-WORM IN A COBRA. D. A. TURKHUD, Indian J. M. Res. **7**:727 (April) 1920.

Turkhud gives a complete summary of the literature on dracontiasis in animals and reports a case occurring in a cobra (*Nada tribudiens*). After the cobra had been in captivity in the laboratory for seven months and while venom was being extracted from it, a loop of worm about 1 mm. thick was noticed to be protruding from a slight swelling on the head. When the worm was examined under a microscope a central uterine tube containing active embryos was noted. These embryos were somewhat smaller than those of the human guinea-worm, but otherwise resembled it closely.

The snake was killed under chloroform and the worm was dissected out commencing at the opening in the swelling. The worm was found lying between the muscles on the back parallel to and along the right side of the spine. With the anterior portion missing, the worm was found to measure 12 cm. in length, ending in a short curved tail. The worm was 1 mm. in breadth, but in all respects resembled the human guinea-worm.

Some whitish fluid was taken from the opening on the head prior to the dissection. This fluid was found to be full of living embryos, somewhat smaller than those of the human guinea-worm, but otherwise resembling these in every respect. Cyclops were then added to the water containing these embryos, and on examination twenty-four hours later, out of twelve cyclops, ten or 83 per cent. showed infection. Fourteen days later, 150 infected cyclops were fed to six healthy cobras, so that each cobra received twenty-five infected cyclops. As a control three healthy cobras were similarly fed, each with twenty-five cyclops infected with embryos of the human guinea-worm. All the cobras died within the subsequent twelve months, but only two showed abnormal postmortem appearances. The first cobra died two and a half months after being fed with cyclops infected with embryos of the cobra guinea-worm. A worm about 3 cm. long and 1 mm. in thickness was found subcutaneously just under the abdominal scales. The second cobra died ten months after it was fed with cyclops infected with embryos of the human guinea-worm. Five worms were found within.

GUTIERREZ, Manila.

CONCERNING THE VIRULENCE OF SPIROCHETES FROM THE SITE OF INFECTION AFTER TREATMENT. FURTHER CONTRIBUTION TO EXPERIMENTAL RABBIT SYPHILIS. L. ARZT and W. KERL, Dermat. Ztschr. **32**:326 (April) 1921.

Three remarkable experiments are cited by the authors. Two patients who had had syphilis and had received sufficient treatment to render them negative serologically presented themselves with erosions at the site of infection. These lesions regressed with no treatment. Examination of serum from the lesions did not reveal any spirochetes, yet inoculations into rabbits were successful. The rabbits developed generalized syphilitic lesions. A third patient had the scar of his lesion surgically removed. He had received treatment with arsphenamin and mercury rubs. The Wassermann reaction was negative. Spirochetes were demonstrated by the dark field and in sections from the scar. Rabbits inoculated with material from this scar developed generalized syphilis, which was transmitted through several passages. When the patient was examined after eight years without treatment, he was found clinically, sero-

logically and neurologically, including all tests on fluid, negative. The first two patients were always negative clinically with no treatment. These experiments are especially significant in relation to the problem of latency. If spirochetes were present in the scars and sites of primary lesions, other foci would have formed during the interval that the patients were without treatment from the period of the beginning of the experiment to the time of reexamination, in one case, eight years later.

GOODMAN, New York.

THE IMPORTANCE OF RECOGNIZING AND TREATING NEUROSYPHILIS IN THE EARLY PERIOD OF THE INFECTION. J. A. FORDYCE, Am. J. Med. Sc. **161**:313 (March) 1921.

A strong plea is made for a spinal fluid test of syphilitic patients before pronouncing them cured. Syphilis of the central nervous system begins probably in the first year of the infection, and in the writer's experience the number of cases corresponds roughly to the number of cases of late neurosyphilis. There is, however, no serologic evidence to show that the spinal fluid is normal in the early stage but becomes infected later.

The importance of spinal fluid examinations is evidenced by the fact that neurosyphilis may be plainly evident, very slight or may present no symptoms at all, and that the usual routine treatment is seldom sufficient to cure the disease, when such involvement has occurred. In fact, symptoms indicating neurosyphilis may be manifest during or shortly after arsphenamin and mercury treatment and call for further treatment, together with intraspinal medication. Experience has shown that the early neurosyphilitic patients can be cured more rapidly, and in the majority of cases cured only by combined intravenous and intraspinal methods. Preference is given to the Swift-Ellis method over reinforcement with minute quantities of arsphenamin.

Patients having a negative spinal fluid with all other tests negative after a thorough and sufficiently prolonged course of treatment can be reasonably assured of future immunity.

JAMIESON, Detroit.

A CONTRIBUTION TO THE STUDY OF CHRONIC ATROPHIC DERMATITIS (ERYTHROMELIE OF PICK; ACRODERMATITIS CHRONICA ATROPHICANS OF HERXHEIMER). PAUTRIER and O. ELIASCHEFF, Ann. de dermat. et syph. **6**:241, 1921.

A typical case of this affection is described, occurring in an otherwise healthy farmer of 38 years. Both lower extremities were involved, the left especially, the lesions being of twenty-two years' duration, and the only subjective symptom being a slight chilling sensation. A biopsy examination was made and is described in detail, its most peculiar feature being a proliferation of the walls of the blood vessels, superficial and deep, resulting in partial occlusion of their lumens. The inflammatory element in the picture is stressed in the discussion, and the authors object to the condition being classed as an idiopathic atrophy.

More commonly found in the colder regions of central Europe, it is suggested that cold may be an etiologic factor, but as these regions also show a prevalence of goiter, the authors believe that thyroid gland disorders may be causative, as is thought to be true of scleroderma. Further observations are needed.

PARKHURST, New York.

EXPERIMENTAL SYPHILIS IN THE RABBIT. VI. AFFECTIONS OF THE BONE, CARTILAGE, TENDONS AND SYNOVIAL MEMBRANES. Part 1. Lesions of the Skeletal System. Part 2. Clinical Aspects of Syphilis of the Skeletal System, Affections of the Cranial Bones and Bones of the Forearm. Part 3. Syphilis of the Posterior Extremities with Other Affections of a Miscellaneous Type. WADE H. BROWN, LOUISE PEARCE and W. D. WITHERBEE, J. Exper. Med. **33**:495 (April) 1921.

Localized infection of bones and tendons was found frequently, especially on the face, feet and legs, most of the lesions arising from the periosteum but also developing from within the bone marrow cavities or epiphyseal lines. Periosteal lesions were either localized masses or were diffuse, showing histologically the typical syphilitic granulomas. Absorption and necrosis of bone were accompaniments of periosteal lesions and were found especially in the facial bones and bones of the feet. Bone lesions were essentially the same as periosteal lesions, but those arising from the marrow cavities were composed chiefly of polyblastic infiltrations.

Lesions of tendons or tendon sheaths were occasionally seen.

The clinical history disclosed the fact that the bone lesions were among the earliest of the generalized forms of the disease, pursued a comparatively rapid course and had no relapse. It was also found that an analogy exists between certain forms of the animal and human affections, this being pronounced in the nasal and epiphyseal lesions in the rabbit compared with congenital syphilis in man. Induced syphilis of the osseous system is capable of being favored or inhibited, according to the experimental conditions employed. Many infections were found which were not accompanied by distinctive signs sufficient to indicate their existence, which might also be analogous to the infections in man when latency exists.

JAMIESON, Detroit.

STUDIES ON X-RAY EFFECTS. VI. EFFECT OF THE CELLULAR REACTION INDUCED BY X-RAYS ON CANCER GRAFTS. J. B. MURPHY, R. G. HUSSEY, W. NAKAHARA and E. STURM, J. Exper. Med. **33**:299 (March) 1921.

An erythema dose of roentgen rays was given on small areas of the groin of mice, and a week later these irradiated areas and also those areas which were not irradiated in the groin opposite were inoculated intracutaneously with a graft of cancer. The irradiated areas showed a low percentage of takes, the protected areas the usual normal amount. If the grafts were introduced subcutaneously they grew equally well in both areas. This could be explained by the histologic examination which showed that a few days after irradiating the skin layers only were markedly infiltrated with round lymphoid cells, this infiltration possibly controlling the grafts made into but not under the skin.

STUDIES ON X-RAY EFFECTS. VII. EFFECT OF SMALL DOSES OF X-RAYS OF LOW PENETRATION ON THE RESISTANCE OF MICE TO TRANSPLANTED CANCER. W. NAKAHARA and J. B. MURPHY, J. Exper. Med. **33**:429 (April) 1921.

After treating mice with small doses of roentgen rays which were capable of producing a lymphoid stimulation, a relatively increased resistance was found to a certain type of transplantable cancer. This increased resistance could be determined in from three to seven days after treatment.

STUDIES ON X-RAY EFFECTS. VIII. INFLUENCE OF CANCER INOCULATION ON THE LYMPHOID STIMULATION INDUCED BY SMALL DOSES OF X-RAYS. W. NAKAHARA and J. B. MURPHY, J. Exper. Med. **33**:433 (April) 1921.

A suppression of lymphoid stimulation occurs if cancer inoculation is performed immediately after exposure to roentgen rays, but if inoculation is delayed for seven days, a second stimulation occurs in a larger proportion of mice so treated. In those treated by the latter method the state of resistance is attended by blood lymphocytosis.

JAMIESON, Detroit.

EXPERIMENTAL MEASLES. F. G. BLAKE and J. D. TRASK, JR., J. A. M. A. **77**:192 (July 16) 1921.

Experimental investigation of the disease in monkeys was conducted for the purpose of devising a method of preventive inoculation. It was found that monkeys are susceptible to the disease, which confirms the contention of Anderson and Goldberger.

Transmission of the disease from monkey to monkey for many generations is readily accomplished by the use of nasopharyngeal washings, citrated and defibrinated whole blood, serum injected subcutaneously, intravenously, and intratracheally, and by intimate contact infection. One attack of experimental measles confers immunity against reinfection.

Blake and Trask found that passage of infection from monkey to monkey by injection of large amounts of blood led to diminution of virulence, thus disappointing their expectation of obtaining a potent "fixed" virus. They determined, however, that the attenuated virus obtained in this way caused a reaction when injected intracutaneously. Their experiments have not reached the stage where it can be said that such local injection consistently causes the development of an active immunity, though in certain instances the development of an effective immunity is indicated.

MICHAEL, Houston, Texas.

STUDIES ON MEASLES. I. SUSCEPTIBILITY OF MONKEYS TO THE VIRUS OF MEASLES. II. SYMPTOMATOLOGY AND PATHOLOGY IN MONKEYS EXPERIMENTALLY INFECTED. H. G. BLAKE and J. D. TRASK, JR., J. Exper. Med. **33**:385 (March) 1921.

It was found that monkeys are susceptible of inoculation with the virus of measles. This was done by intratracheal injection of filtered and unfiltered nasopharyngeal washings of patients with measles, and a relatively constant group of symptoms was induced which closely resembled measles in man.

The symptoms and course of the disease closely parallel those in man, and the microscopic pathology of the skin and mucous membrane lesions are practically identical with the corresponding human lesions.

JAMIESON, Detroit.

STUDIES ON MEASLES. III. ACQUIRED IMMUNITY FOLLOWING EXPERIMENTAL MEASLES. F. G. BLAKE and J. D. TRASK, JR., J. Exper. Med. **33**:621 (May) 1921.

This work shows that the effect of measles in monkeys is the same as in man, one attack producing immunity to reinfection. The result is the same whether heterologous or homologous virus is used or whether intravenous or mucous membrane inoculation is used.

JAMIESON, Detroit.

MULTIPLE CARCINOMA OF THE SKIN: "PRECANCEROUS DERMATOSIS OF BOWEN." J. H. Sequeira, Brit. J. Dermat. & Syph. **33**: 173 (May) 1921.

Sequeira describes a case of precancerous dermatosis of Bowen occurring in a woman who was 57 years of age when first seen in 1912. At that time she had several tumor lesions on the forehead, which disappeared following radium treatment. She returned in 1920 presenting lesions on the left arm, right thigh, back, the front of the trunk and right knee, while the forehead showed a broad crescentic area of scarring, with a few palpable, pinhead sized, slightly raised thickenings. The lesion on the left arm, which appeared as a nodular irregularly-shaped excrescence, had been present for four months, while that on the right thigh was a button-like skin tumor with a broad base, rounded edge and granular surface. The growths on the back, which appeared in 1912, varied from small tumors to large excrescences, two of the patches looking not unlike those of Paget's disease.

The article, which is to be continued, also contains a résumé of the cases reported by Bowen and Darier.

Senear, Chicago.

SUPERINFECTION IN EXPERIMENTAL SYPHILIS FOLLOWING THE ADMINISTRATION OF SUBCURATIVE DOSES OF ARSPHENAMIN OR NEO-ARSPHENAMIN. Wade H. Brown and Louise Pearce, J. Exper. Med. **33**:553 (May) 1921.

Animals used in these experiments were inoculated and reinoculated with a virus of essentially the same virulence and eighteen days later were treated with original arsphenamin and neo-arsphenamin (6 mg. and 9 mg. per kilo, respectively). This dose was chosen for the purpose of producing definite regression of lesions with a relapse two or three months later. Five days after treatment these animals and untreated controls were reinoculated with the same original virus. Relapses occurred in all treated but not reinoculated patients, showing that the dose was subcurative. In the reinoculation of infected controls the majority of lesions were of a nonspecific inflammatory type, possibly a slight local infection. On the other hand, all but two of the reinoculated treated animals developed typical chancres, in most instances the second chancre overgrowing recurrence of the original lesions.

They conclude that in animals the presence of *Spirochaeta pallida* does not prevent the possibility of a second infection with the same organism. As this state may be induced experimentally by treatment with arsphenamin or neo-arsphenamin, insufficiently treated or uncured patients may be rendered as susceptible to a second infection as a normal person, the manifestations being indistinguishable from those of the original infection.

Jamieson, Detroit.

EPITHELIOMA OF THE HAND WITH A TENDENCY TO SPONTANEOUS CURE. C. E. Corlette and Keith Inglis, M. J. Australia **1**:250 (March) 1921.

The case reported is that of a man 63 years old, suffering from a lesion of nine months' duration. This lesion started as a small sore on the dorsum of the left hand near the metacarpophalangeal joint of the middle finger. The

sore being treated, healed, leaving a ridge at the margin. This ridge continued to advance, the center healing as the periphery advanced. At the time of examination the lesion was found spreading from the base of the thumb across the hand, just below the wrist joint and ending near the base of the ring finger where it was rough, irregular and almost horny. The lesion was not attached to the deeper structures. There was no glandular enlargement. The center appeared to be healed scar tissue. The Wassermann reaction was negative at two different times. Microscopic examinations of serum from the lesion was negative for spirochetes in the dark field. Examination for bacteria or other parasites was negative. Histologic sections both before and after operation were those of epithelioma. The patient made a complete recovery.

GUTIERREZ, Manila.

STUDIES IN FAMILIAL NEUROSYPHILIS. I. CONJUGAL NEUROSYPHILIS. J. E. MOORE and A. KEIDEL, J. A. M. A. **77**:1 (July 2) 1921.

Fifty-two partners of fifty neurosyphilitic patients were examined by these investigators. The examination included a careful anamnesis, physical and neurologic study, a Wassermann reaction of the blood, and cell count, globulin, Wassermann and colloidal tests of the cerebrospinal fluid. Of the whole number of fifty-two partners, forty were syphilitic, and of these, twenty-one had neurosyphilis. Of the twenty-one instances of neurosyphilis, the type was similar in both partners eight times; three couples had paresis, two had tabes, and three cerebrospinal syphilis of the same type.

The authors obtained a higher percentage of conjugal neurosyphilis than previous investigators, but this is attributed to the routine investigation of the spinal fluid. Routine examination of the partners of neurosyphilitics is of practical value. That spinal fluid examination is an indispensable part of the routine is indicated by the discovery of asymptomatic neurosyphilis in seven partners.

The authors feel that their study does not justify any decision as to the duality of spirochetal strains.

MICHAEL, Houston, Texas.

SILVER-ARSPHENAMIN. ESCHER, Ann. de dermat. et syph. **5**:203 and **6**:257, 1921.

In an exhaustive manner, with a bibliography including fifty-two articles, the author considers the chemical structure, physical and chemical properties, dosage and curative power of the new arsenical. Much of the material for this article was secured from the Medical Corps of the American Expeditionary Forces in Germany, and has already been incorporated in a similar paper, with a similar bibliography, by Walson (Silver-Salvarsan in the Treatment of Syphilis, *Am. J. Med. Sc.* **3**:418, 1921). Unlike Walson, however, Escher mentions the frequency with which icterus has followed this new medication in the hands of some workers. He also relates three cases of fatality which he has found in the literature, hemorrhagic encephalitis having been the terminal event in three and pneumonia following a generalized dermatitis in the fourth.

Escher concludes that in silver-arsphenamin we have a valuable new drug, whose toxicity is lower than that of arsphenamin, and whose therapeutic powers at least equal those of arsphenamin and surpass those of neo-arsphena-

min, sodium-arsphenamin and arsphenamin-sulphoxylate. In neurosyphilis the results of its use are said to be excellent, but the author advises against undue enthusiasm until time and careful observation have proved this.

PARKHURST, New York.

TWO CASES OF CONGENITAL ACANTHOSIS NIGRICANS WITH DIABETES MELLITUS. GUIDO MIESCHER, Dermat. Ztschr. **32**:276 (April) 1921.

A unique instance of familial acanthosis nigricans is reported. Two children, a boy and a girl, presented since birth lesions of the skin characteristic of the disease. The father presented nevoid lesions which were histologically indistinguishable from acanthosis nigricans. In addition to the skin lesions, the children were not normal in other respects. They both had diabetes mellitus. The mental development was retarded, and they were distinctly imbecile. Lanugo hairs were profuse. The girl had not yet begun to menstruate, although 19 years of age. The boy also had a condition of the scalp considered cutis verticis gyrata. The question of etiology and the distinction between benign and malignant cases of the disease are discussed. It seems inappropriate to classify cases as benign and malignant because the adjective can only refer to the underlying cause, as for example, carcinoma. Those instances of the disease which are congenital, and the number is growing, cannot depend on such etiology, and cases such as the two presented lend credence to the idea that some disturbance of glands of internal secretion which have to do with the development of the skin is the underlying cause in such cases.

GOODMAN, New York.

STUDIES ON DECREASING THE REACTION OF NORMAL SKIN TO DESTRUCTIVE DOSES OF X-RAYS BY PHARMACOLOGICAL MEANS AND ON THE MECHANISM INVOLVED. J. AUER and W. D. WITHERBEE, J. Exper. Med. **33**:791 (June) 1921.

Using four groups of rabbits, roentgen-ray treatment of 30 skin units was administered on the ears of the rabbits. Normal rabbits composed the first group; rabbits injected intraperitoneally with 10 c.c. of horse serum thirteen days after roentgen-ray treatment formed the second group; the third group was composed of rabbits treated by two subcutaneous and two intramuscular injections of 1 c.c. of horse serum each at three to four day intervals followed in ten days by roentgen-ray treatment; the fourth group was made up of rabbits prepared as Group 3 but reinjected with 10 c.c. of horse serum thirteen days after treatment.

It was found that the usual changes followed by local gangrene developed in the normal rabbits in about thirty-three days; in the second group in from thirty-six to fifty days; in the fourth or sensitized reinjected group in from fifty to eighty-five days; but in the sensitized animals of Group 3 the results appeared in from forty-six days (one animal) to no gangrene even after 340 days.

This remarkable immunity to lethal doses of roentgen rays is explained on the assumption that in the sensitized animals there are still anaphylactic bodies present bound to the cells of the treated area, these bodies disappearing following the injection of serum after the roentgen-ray treatment.

JAMIESON, Detroit.

TWO NEW CASES SHOWING THE COINCIDENCE OF NERVOUS AND NON-NERVOUS MANIFESTATIONS IN A SYPHILITIC PERSON. SIMON, Bull. Soc. franç. de dermat. et syph. **5**:165, 1921.

In a man, aged 25 years, who presented supposedly tertiary syphilitic involvement of the penis and inguinal lymph nodes, both Achilles reflexes were absent. The spinal fluid findings were negative.

A man, aged 33 years, presented a costal osteoperiostitis and a facial paralysis. Nothing is said of the spinal fluid. It is not unlikely that the paralysis was due to the pressure of a periostitis in the fallopian canal.

Neither case seems conclusive, but they were presented to stimulate discussion regarding spirochetal strains. Queyrat suggests that in each case of early syphilis the exact morphology of the spirochetes be noted and kept in mind as the progress of the case is observed; it is possible that a certain type may be found to cause lesions of the nervous system.

PARKHURST, New York.

PARESIS TREATMENT BY ARSPHENAMIN AND MERCURY. C. A. BONNER, Boston M. & S. J. **185**:60 (July 14) 921.

This article contains a rather general discussion of the treatment of paresis by the intravenous injection of arsphenamin in a series of cases treated at the Warren State Hospital, Pennsylvania. Results at the end of two years are given.

LANE, Boston.

THE A B C OF RADIUM. ERNEST M. DELAND, Boston M. & S. J. **184**: 696 (June 30) 1921.

This article contains a discussion of the physics of radium, the technic of radium therapy, the methods used at the Huntington Memorial Hospital, Boston, the effects on tissue, and general indications for radium treatment, both superficial and deep.

LANE, Boston.

EFFECT OF SMALL DOSES OF X-RAYS ON HYPERTROPHIED TONSILS AND OTHER LYMPHOID STRUCTURES OF THE NASOPHARYNX. J. B. MURPHY, W. D. WITHERBEE, S. L. CRAIG, R. G. HUSSEY and E. STURM, J. Exper. Med. **33**:815 (June) 1921.

Using a dose of roentgen rays equivalent to from 1 to 1¾ skin units (filtered through 3 mm. of aluminum), the writers state that atrophy of the tonsils and adjacent lymphoid structures can be accomplished. An area about 3 inches square under the angle of the jaw on each side is exposed with this dose, which is repeated in a few weeks if necessary. The degree of atrophy can be determined by experience, and such treatment does not prevent surgical removal if sufficient reduction does not follow. In all but three or four cases one treatment was sufficient, improvement probably following improved drainage resulting from atrophy of the lymphoid tissue.

JAMIESON, Detroit.

DARIER'S DISEASE. HUDELO, BIGOT and CAILLAU, Bull. Soc. franç. de dermat. et syph. **5**:159, 1921.

A boy, 16 years of age, presented keratotic lesions on the forehead, behind the ears, about the jaws, along the nasolabial folds and beneath the clavicles.

The microscope confirmed the diagnosis of follicular dyskeratosis, some of the lesions, however, being nonfollicular.

It is of interest to note that this patient had first appeared, in July, 1920, with an eczema of the scalp and face and a pronounced keratosis pilaris of the extremities. There was then no sign of Darier's disease, which appeared later while tar preparations were being used to combat the eczema.

Darier recommends polyglandular endocrine treatment.

PARKHURST, New York.

ANTIVENEREAL PROPHYLACTICS; RELIABILITY AND EFFECT. J. SCHUMACHER, Deutsch. med. Wchnschr. **47**:626 (June) 1921.

The author recommends a 1:1,000 solution of mercuric chlorid as the most effective antisyphilitic prophylactic. The penis should be well bathed, especially the fossa navicularis. The widespread calomel ointment has no reliable disinfecting power at all—as it is nonsoluble and lacks free mercury ions which alone guarantee disinfection. For gonorrhea a 1 per cent. solution of albargin proved most effective. The penis should be well bathed in this solution—injection is not necessary—but a match mounted with wadding well soaked in albargin should be used for wiping out the fossa navicularis.

AHLSWEDE, Hamburg.

A NEO-ARSPHENAMIN FATALITY. NICOLAS and J. LACASSAGNE, Ann. de dermat. et syph. **6**:280, 1921.

A strong Italian girl of 20 years, under treatment for a secondary papulosquamous syphilitic eruption, had received an initial injection of 0.3 gm. of neo-arsphenamin; a week later a second injection, amounting to 0.45 gm. was given. A large ampule was used, containing 0.9 gm., the distilled water being placed in the ampule to dissolve the powder; the remaining 0.45 gm. was administered to another patient. Two days later the girl developed nervous symptoms, with respiratory disturbance, coma and convulsions, death ensuing within twenty-four hours. The other patient experienced no reaction; therefore this fatality seems to be due to a reaction of the individual, and not to any toxicity of the neo-arsphenamin.

PARKHURST, New York.

DOSAGE OF ARSPHENAMIN. K. BIELE, Deutsch. med. Wchnschr. **47**:619 (June) 1921.

A woman of 26 was given 3 gm. of neo-arsphenamin in one injection by mistake instead of 0.3 gm. Previously she had received 0.45 gm. of neo-arsphenamin and had undergone a two course treatment with mercury. The patient showed slight symptoms of intoxication until the fifth day after injection and then fully recovered. The Wassermann reaction was still positive one week after the injection; it turned negative, however, without further treatment five weeks later.

AHLSWEDE, Hamburg.

MACULAR ATROPHY OF THE SKIN. HUDELO and WALTER, Bull. Soc. franç. de dermat. et syph. **5**:162, 1921.

A girl, 21 years of age, had noticed unusual redness of the cheeks and chin eight months previously. At present there was a palm-sized patch on the thorax, made up of pallid, atrophic macules on a reddish background that

was slightly squamous. The face and the lumbar spine showed similar macules, much less marked. There were no subjective symptoms; the sensations were not disturbed.

Several diagnoses were considered, including atrophic lichen planus, white spot disease, Jadassohn's anetoderma and atypical parapsoriasis, but a biopsy examination was thought to be the only means of settling the question. To further complicate the picture, an atrophic spot was found on the palate.

PARKHURST, New York.

STUDIES ON LYMPHOID ACTIVITY. V. RELATION BETWEEN THE TIME AND EXTENT OF LYMPHOID STIMULATION INDUCED BY PHYSICAL AGENTS AND THE DEGREE OF RESISTANCE TO CANCER IN MICE. J. B. MURPHY, W. NAKAHARA and E. STURM, J. Exper. Med. **33**:423 (April) 1921.

Heat or small doses of roentgen rays are capable of stimulating lymphoid tissue to greater resistance to transplanted cancer. The former is sluggish at first, then latent, and is later more pronounced; the latter produces a sharp depression followed by a marked stimulation lasting a longer time. Inoculation of cancer at the height of the stimulation phase shows marked resistance with both roentgen rays and heat.

JAMIESON, Detroit.

LUPUS VULGARIS OF THE FACE WITH NASAL HYPERTROPHY SIMULATING RHINOPHYMA. G. THIBIERGE and RABUT, Bull. Soc. franç. de dermat. et syph. **5**:176, 921.

A woman, aged 58 years, since 1910 had had lupus vulgaris of the cheeks, which had been cauterized. In 1916 her nose became dusky red, large and crusted, showing nodules. When shown, the lesions of the cheeks were again active, and the tip of the nose, measuring 5 cm. in its transverse diameter, was violaceous, smooth and soft, with no nodules but many superficial scars. There was no tendency to destruction of the part. The cervical lymph nodes were palpable. The nasal enlargement was attributed to a chronic lymphangitis, such as often affects the lip.

Darier advises a biopsy and animal inoculations to verify the diagnosis.

PARKHURST, New York.

INVESTIGATION OF LIVER FUNCTION IN SYPHILITICS, WITH ESPECIAL REFERENCE TO ICTERUS SYPHILITICUS PRAECOX AND ARSPHENAMIN LIVER DISTURBANCES. PAUL TACHAU, Dermat. Ztschr. **32**:305 (April) 1921.

The author sought to get an idea of the liver function in icterus syphiliticus praecox by blood chemistry studies. There is a definite derangement of carbohydrates. From this it seems that Buschke was right in claiming a damage of the liver parenchyma through spirochete toxins. No pathologic blood chemical findings, as far as carbohydrate was concerned, could be determined for congenital syphilitic infants. Although the few cases studied of liver function among syphilitic patients treated with combinations of mercury and arsphenamin do not warrant conclusions, Tachau did not find any harmful effects of such a combination in treatment.

GOODMAN, New York.

ROENTGENOTHERAPY OF ACTINOMYCOSIS. A. E. RUETE, Dermat. Ztschr. **32**:344 (April) 1921.

Ruete has found that doses as large as those recommended by Klemm in an earlier number of the *Zeitschrift* are unnecessary. He gives dosages of approximately one third less with good results. The measurements are given in a foreign scale, probably Kienbeck's, as follows: Klemm recommends two sessions at 20 cm. skin-focus distance with 3 mm. of aluminum for 27 X repeated five times to a total of 100 X. Ruete's patients received a total of 35 X. This was repeated in deep seated cases. The argument is advanced that roentgenotherapy should be accomplished with the smallest dosage which is effective.

GOODMAN, New York.

TREATMENT OF FURUNCULOSIS IN INFANTS. C. G. GRULEE and C. B. ROSE, J. A. M. A. **77**:37 (July 2) 1921.

Impressed with the inadequacy of the commonly used methods for treating this condition, the authors have tried roentgen-ray treatment. After some experience they found that a soft unfiltered ray (3 milliamperes, 6 inch spark gap, 9 inch focal distance, for one minute) was best. Their general impression as to the results of roentgen-ray treatment has been, on the whole, favorable; but their cases have been too few to reach definite conclusions. They feel, however, that the proper use of the roentgen ray may add materially to the efficacy of treatment for furunculosis in babies.

MICHAEL, Houston, Texas.

ACCIDENT AS THE CAUSE OF ACRODERMATITIS ATROPHICANS AND ARTHRITIS DEFORMANS. E. MEIROWSKY, Dermat. Ztschr. **32**:346 (April) 1921.

A young soldier who was admitted to the Army free of any defects developed typical acrodermatitis chronica atrophicans and arthritis deformans after an accident to his foot. In what fashion the accident caused the acrodermatitis is difficult to decide. The answer of trophoneurosis is the one usually given.

GOODMAN, New York.

THE TESTES AND CERTAIN VASOMOTOR REACTIONS OF THE PENIS. A. C. CRAWFORD and J. M. GEORGE, J. Urol. **5**:89 (Feb.) 1921.

The authors' work consisted in experimentation on dogs, using various drugs as well as testicular and other tissue extracts, to determine the constrictor or dilator action on the penis. They conclude that the testes have a specific substance that produces such dilatation.

JAMIESON, Detroit.

A METHOD OF DEMONSTRATING CATALYTIC ENZYMES IN INFECTED HAIRS. T. H. C. BENIANS, Proc. Roy. Soc. **14**:69 (June) 1921.

The suspected hair is placed in about twenty volumes of hydrogen peroxid on a slide and under a cover slip. When tinea infection is present, a vigorous effervescence persists for from fifteen to thirty minutes. The root of the hair must not be included because it normally will effervesce. (The same

reaction may be expected in other infections in which "catalytic" enzymes are present, and therefore the method can hardly be of value in differential diagnosis.)

GUY, Pittsburgh.

IDIOPATHIC PURPURA WITH UNUSUAL FEATURES. A. S. ROSENFELD, Arch. Int. Med. **27**:465 (April) 1921.

Two cases are described by the writer which showed a familial tendency and repeated joint hemorrhages which had an association with the symptoms of Henoch's purpura. One case also had a spontaneous fracture.

JAMIESON, Detroit.

DERMATITIS HERPETIFORMIS. E. G. LITTLE, Proc. Roy. Soc. **14**:69 (June) 1921.

A woman who had been bitten on the finger by a rat six years previously and had had a resultant rat-bite fever that persisted for a year developed an extensive eruption of vesicles with pigmentation and intense itching a year later. A pronounced indicanuria and a marked eosinophilia were noted. The patient was unusually susceptible to arsenic so that proper medication was a problem.

GUY, Pittsburgh.

A CASE OF ACRODYNIA. P. W. EMERSON, J. A. M. A. **77**:285 (July 23) 1921.

A boy, aged 4½, developed general weakness, loss of knee reflexes and redness and peeling of the finger tips and toes; the redness, extending over half the first joint, diminished gradually from the tip backward. On one toe, there was a vesicle-like lesion. The constitutional disturbances consisted of marked apathy and muscular weakness, with moderate fever.

Complete recovery ensued in about four months.

MICHAEL, Houston, Texas.

RADIUM BURN. E. G. LITTLE, Proc. Roy. Soc. **14**:68 (June) 1921.

A man, aged 50, who had had radium applied over his spine for twenty-four hours, ten years ago, developed an extensive scar which three months ago broke down to form a deep ulcer. The presenter considered the condition malignant.

GUY, Pittsburgh.

TREATMENT OF WEEPING ECZEMAS WITH LENIGALLOL. L. ISAACSON, Deutsch. med. Wchnschr. **47**:653 (June) 1921.

Lenigallol, a compound of acetic acid and pyrogallic acid, is used in the following ointment:

	gm. or c.c.
Lenigallol	1.5
Zinc oxid	
Olive oil	āā ad 25.0

AHLSWEDE, Hamburg.

Society Transactions

AMERICAN DERMATOLOGICAL ASSOCIATION

Clinical Session, June 2-4, 1921

JAY FRANK SCHAMBERG, M.D., *Presiding*

ULCERATIONS OF THE LOWER LIP. Presented by DR. WHITE.

A man, aged 52 years, had been in the United States Navy for twenty-five years, had traveled all over the world and had passed the Island of Guam, but had never stopped there. He had had ample opportunity to contract some tropical disease. The disorder began five years ago in Cuba after he had wounded the lip by rapidly removing a clay pipe. He had received treatment of all kinds, including arsphenamin, to no effect. The case had been investigated by many different men, and the navy department had sent tissue to Washington, D. C., for examination, but nothing had been found outside of "chronic inflammatory" tissue.

The condition was thoroughly enigmatic objectively. The lower lip had entirely disappeared, and the remaining tissue disclosed nothing which indicated any of our well-recognized diseases. Wassermann tests had always proved negative.

DISCUSSION

No diagnosis was offered.

MULTIPLE XANTHOMA. Presented by DR. TOWLE.

A boy, aged 3 years, had had an affection since earliest infancy. As seen, it involved the scalp, neck, trunk and extremities. At first few, the tumors had gradually increased in number and had involved more and more territory. The primary lesion was small, perhaps pea-sized and by steady gradual growth, it had attained a maximum size of about 1½ by 1 inch. Some of the lesions were round, though many were oval in shape. Their tops were rounded so that in some it was fully one-half inch from the highest point to the level of the surrounding skin. In shape the lesion reminded one strongly of a beetle. The color was a curious yellow. To the touch, the tumors were firm although not hard. Histologically the tumors were xanthoma.

As to treatment, under heliotherapy a number of the tumors had disappeared. Others had shrunk in varying degree.

DISCUSSION

DR. PUSEY agreed with the diagnosis. He thought that Dr. Towle and Dr. White should receive an expression of appreciation for the opportunity of seeing their patients. Dr. Towle's case was unique so far as manifestations of xanthoma were concerned in his experience. He asked whether there was any disturbance in the general health.

DR. TOWLE said that the diagnosis had been confirmed by histologic sections. Some of the lesions had disappeared under heliotherapy. There was no disturbance in general health, but the cholesterol content of the blood was very high, three times that of the normal child of that age.

MULTIPLE PIGMENTED NEVI. Presented by Dr. Oliver.

A boy, aged 1 year, presented numerous unusually black nevi scattered over the body. The largest single lesion covered the entire back. The lesions had been present since birth and were of inky blackness. The skin appeared normal except for the pigmentation.

DISCUSSION

Dr. Ravogli said he had seen three or four cases of melanosarcoma which had started from nevi, black pigmented spots spread all over, and the patients had died within a short time. He thought this was a case of melanosarcoma.

CONGENITAL ALOPECIA. Presented by Dr. White.

A boy, aged 2 years, had complete alopecia. The nails and teeth were normal. There were no similar cases in the family history.

DISCUSSION

Dr. McEwen called attention to the reports of congenital alopecia by Dr. Hyde, in which two of the patients had webbed toes.

EPIDERMOLYSIS BULLOSA (AVEC KYSTES EPIDERMIQUES). Presented by Dr. White.

The patient was a child, aged 2 years. The disease began at the age of 5 days and had persisted ever since. In addition to the bullae which had often been hemorrhagic, the child presented the "kystes epidermiques" of Hallopeau. The knees, elbows and knuckles were a mass of contiguous, cigaret-paper like, pea-sized scars. Many of the nails were gone, and at presentation there was a hemorrhagic bulla on the palm as the result of a fall on the previous day.

Thyroid therapy had been started on May 25, and the mother stated that since that time there had been fewer bullae and that the child's condition was better.

DISCUSSION

Dr. Sutton was interested in this condition because of the curious histologic picture (absence of elastic fibers) presented by many, if not all, of the patients with congenital cases. He believed, however, that Dr. Fred Wise had failed to find this anomaly in the cases that had developed in adult life.

With regard to the spelling of the term, fourteen years ago, he had discussed the matter with Dr. Achilles Rose of New York, at that time probably our greatest living authority on medical nomenclature, and Dr. Rose had informed him that it should be "epidermidolysis bullosa" and not "epidermolysis bullosa."

CONGENITAL ALOPECIA. Presented by Dr. Towle.

A boy, aged 2 years, presented a complete absence of hair on the scalp, eyebrows and elsewhere on the body. There was also a certain dystrophy of the nails and a tendency toward recurrent paronychia. From time to time lanugo hairs had appeared, whose life, however, was short. At no time had there been any normal hair.

DISCUSSION

Dr. Wende recalled that at a meeting in Boston in 1902 he read a paper describing a similar case—almost a counterpart—under the title of "Epi-

dermolysis Bullosa Hereditaria," with congenital alopecia, dystrophy of the nails and inflamed areas about the mouth. The condition about the mouth he thought was due to the irritation of the skin as the child drooled; the drooling being due to the irritation and bleb formation within the mouth as the result of food trauma. The rarity of this disease is great; apart from Dr. Towle's case he could recall only one other; reported in the ARCHIVES. These three cases all have the same external clinical features and undoubtedly should be classed as "epidermolysis bullosa hereditaria."

RINGWORM. Presented by DR. WHITE.

A boy, aged 7 years, who presented a type of ringworm not often seen in Boston, came in with a few pustules, or pustular remains, and all around the bald, slightly infiltrated, dull red center there was a rim of crusting. On cultivation violaceous growths were produced.

EPIDERMOPHYTOSIS. Presented by DR. WHITE.

A man, aged 50 years, had had the disorder constantly on the feet for five years, whereas on the hands it had developed more recently and had come and gone. At the time of presentation he had a severe outbreak presenting a contiguous mass of pinhead-sized or smaller vesicles on the lateral aspects of the fingers and on the adjacent palms and backs of the hands and fingers. The itching was intense. The feet were less intensely affected. Here there was mild vesiculation about the toe and exfoliation extending backward onto the ball of the feet.

DISCUSSION

DR. WILLIAMS thought such a case was very interesting, particularly the presence of the disease on the sole under the instep. It was hard to conceive of the organism spreading so rapidly as to involve both hands and feet in a few hours, but the rapid spread of the eruption does occur. He thought that a better explanation of the spread of the eruption was the distribution by the circulation of toxin absorbed from the primary focus of the disease. He thought chances of finding the organism of the lesions of the feet were much greater than in those of the hands, and he believed the condition on the latter was toxic rather than mycotic.

DR. RAVOGLI thought it was a case of occupational dermatitis. The man worked seven days a week in a shoe factory, and probably in handling the leather would irritate the skin and produce a dermatitis.

DR. WENDE thought every one should be familiar with this type of eruption as it was characteristic of the epidermophyton eruptions.

MYXEDEMA. Presented by DR. TOWLE.

A woman, aged about 35 years, for several years had been under treatment at the Massachusetts General Hospital for myxedema and had been under constant thyroid therapy. For some months there had been recurrent swellings on both cheeks, which had come and gone with irregularity. The present manifestations had been present for about two months. On both cheeks, over the flush areas, were patches of considerable size, which had the clinical characteristics of acute lupus erythematosus.

DISCUSSION

DR. HIGHMAN thought the lesions looked like lupus erythematosus, and asked whether there had been any improvement.

DR. GOLDENBERG thought it was a superficial type of lupus erythematosus.

DR. WILLIAMS thought the spots just below the ear were almost a counterpart of a case presented recently by Dr. Whitehouse. He agreed with Dr. Goldenberg that it was lupus erythematosus, and doubted whether there was any connection with the thyroid gland. He was particularly interested in the presence of the small papule in the right cheek. This resembled rosacea, but was not the same. The case of Dr. Whitehouse presented papules sometimes covered with a crust, and Dr. Williams wished to know whether the other gentlemen had seen an eruption of soft papules of this type in connection with lupus erythematosus.

DR. TOWLE said the patient was shown because of a deficient thyroid gland. She was taking thyroid extract all the time, and the eruption developed during this medication. He wished to contrast this patient with the child whose eruption had cleared up following thyroid therapy, in an effort to determine if possible whether there was any connection between hypothyroidism and the eruption.

LYMPHANGIOMA OF THE TONGUE. Presented by DR. OLIVER.

The patient was a man aged 28 years, whose lesion, which had persisted for five or six years, involved practically the whole tongue. The tongue was twice its normal size.

The patient was to be placed on radiotherapy.

DISCUSSION

DR. COLE said they had recently had two cases like this at Lakeside Hospital. One of the men from the Mayo Clinic had said that better results were obtained with roentgen rays than with radium. Roentgenotherapy had been used in his cases with good results. One patient was a girl, aged 5 years, with a lymphangioma which involved the right side of the tongue so extensively that she could not get the tongue back in the mouth. She was given two treatments with roentgen rays, two weeks apart, a small dose being used and no especial cross-firing. There was a marked change after the first treatment, and the child could now get her tongue back in her mouth. He suggested the use of roentgenotherapy rather than radium in this case.

DR. PUSEY said he thought there was no difference in the results with radium and roentgen rays, except as the amount of soft rays would vary. He thought it was important to get essential facts in mind. In his judgment, so far as the actinic effects were concerned, there was no difference. He would prefer radium in this case because it was more convenient to use, but the essential thing was that there was no difference in the actinic effect in the two agents. In his opinion the more unnecessary confusion that was avoided, the less trouble there would be in the future with the two agents.

TUBERCULOSIS. MULTIPLE FORMS IN A SINGLE PATIENT. Presented by DR. TOWLE.

A colored woman, aged 23 years, originally had a scrofulous gland on the right side, and traces of the scrofulous tuberculosis were still visible. Later there had developed a tuberculosis cutis of the right lower lid involving the

tear duct and gland, which still showed activity. On the right cheek was a large patch of typical lupus vulgaris. On the left forearm was a hard brownish-red nodule the size of a small pea, which represented the persisting local reaction to tuberculin injections.

EPITHELIOMA OF THE CHEEK. Presented by Dr. C. Guy Lane.

A man, aged 67 years, showed a healed epithelioma of the cheek. The lesion had been present on his left cheek for eight years when he was first seen at the clinic eight months previously. At that time the tumor was about 1 by 1½ inches in size, crusted, hard and elevated one-half inch above the surface. He had received seven hours of radium therapy with a half strength applicator unscreened, and two hours of treatment with the same applicator using a 0.3 mm. brass screen. The lesion now showed a smooth, purplish healed scar without any crust and without any sign of induration.

MYCOSIS FUNGOIDES. Presented by Dr. Towle.

A woman, aged 50 years, had had the disorder for three years. When she presented herself three years previously, the body was covered with almond-sized, hard, resistent tumors. Several of the growths had been excised, and all gave the picture of mycosis fungoides. The skin surrounding the lesions was dry and flaky, and from the skin arose the little masses, perhaps a dozen in one area, then an open space and then another group. Stains of old lesions were still visible.

Roentgenotherapy had been used exclusively, and under its influence the disease had largely cleared up. No new lesions had developed in several months. The treatments, of which she had received ten or twelve, were each of ⅛ or 1/10 unit, the highest dose having been ¼ unit. She had had some reaction following treatment, and the smaller doses worked better than the larger ones. The reaction consisted of an erythema which resembled sunburn, then actual vesiculation, the changes occurring within twenty-four hours after treatment.

PITYRIASIS RUBRA PILARIS. Presented by Dr. Oliver.

A woman, aged 53 years, had had the disorder for nine months. It appeared immediately after a severe shock. It began on the forehead and had gradually spread until it involved practically the entire body; it was still spreading.

The use of the quartz light had relieved the itching and thinned out the skin to some extent.

ACUTE LUPUS ERYTHEMATOSUS. Presented by Dr. Towle.

A woman presented lesions of lupus erythematosus of the acute, diffuse type. The disorder was of four months' duration.

DISCUSSION

Dr. Sutton said he did not know the cause of lupus erythematosus. This patient undoubtedly was suffering with several bad teeth, and he believed the teeth should be roentgenographed. It was always well to clear up all foci of infection. The fact that lupus erythematosus is practically unknown in the sanatoriums around Denver would indicate that it was not necessarily related to tuber-

culosis. Dr. Hartzell has reported a case that was cured following the removal of infected teeth. Dr. Sutton made it a point to remove infected tonsils and infected teeth; he had obtained some good results; he was sure a much larger percentage of recoveries had taken place since they had followed this plan.

Dr. McEwen stated that in the *British Journal of Dermatology* a number of reports by Barber had appeared in the last year in which *Streptococcus longus* had been found in culture of the stools and in the tonsils; vaccines prepared from cultures had caused reactions locally in the areas involved.

Dr. Highman said he had seen several cases of lupus erythematosus in patients with full sets of false teeth.

Dr. Chipman, in answer to Dr. Highman's remark, said he had seen people who wore two complete plates of teeth and yet focal infection was seen underneath, because the mere extraction of teeth does not necessarily eradicate focal infection. He thought this of great importance in lupus erythematosus. The most dramatic dermatologic result he had ever seen was the disappearance of lupus following the surgical removal of six or seven teeth. He believed the profession was guilty of serious laxity when the foci were attacked by simple extraction. The teeth should be surgically removed in the proper manner.

Dr. John E. Lane took exception to Dr. Sutton's remarks in which he intimated that because lupus erythematosus is not frequent in tuberculosis sanatoriums it is not a tuberculous process. He considered that argument of no value because skin tuberculosis of any description is quite rare in tuberculosis sanatoriums. He had looked for it in several, and had made many inquiries as to its frequency of physicians in charge of such sanatorium. The question of the relationship of lupus erythematosus to tuberculosis would have to be settled in some other way.

EPITHELIOMA OF THE WRIST. KERATOSIS OF THE FACE.

Presented by Dr. Towle.

On the face of a woman aged 64 years were some ordinary keratoses. On the wrist was a large ulcerative lesion which offered considerable difficulty in diagnosis, which was only cleared up by the microscope. The lesion consisted of concentric whorls of hard epithelial ridges enclosing a central, crusted ulcer. The whole was considerably raised above the general surface and was nearly 3 inches in diameter.

At first the diagnosis of a manifestation of syphilis was considered, but the microscope revealed that it was a basal-cell epithelioma.

A CASE FOR DIAGNOSIS.

Presented by Dr. Towle.

A woman, aged 63 years, was seen for the first time on the day of presentation. She had been in the hospital before for treatment of a throat condition, which proved to be an epithelioma. The interesting part was that the lesion looked like lupus vulgaris, and, although it had been present only three years, it had degenerated into an epithelioma.

There was complete destruction of the uvula, which it was thought was caused by tuberculosis. The alae of the nose showed extensive ulcerative tuberculosis. On the right cheek was also a coin-sized ulcerative ulcer. No active tuberculosis was found in the lungs, although with the roentgen ray there were signs indicative of an old, healed process.

DISCUSSION

DR. PUSEY thought it was syphilis.

DR. POLLITZER thought it was tuberculosis.

DR. MCEWEN asked whether the condition of the tongue had been proved to be carcinoma.

DR. CORLETT thought that in hazarding an opinion as to the diagnosis, the first would be syphilis and the next tuberculosis.

DR. TOWLE said the condition for which the woman had first entered the hospital was an epithelioma. He thought the present condition was due to tuberculosis, as there was neither history nor evidence of syphilitic infection.

LESIONS ON THE EAR, NECK AND BACK OF THE SHOULDER.

Presented by DR. SMITH.

A woman, aged 47 years, when first seen had lesions back of the ear like the large, shiny papular lesions of syphilis. There were large, circinate lesions on the inside of the thighs and over the left breast. There was no history of syphilitic infection, but on the possibility of its being syphilis she was given four or five injections of arsphenamin, without any particular effect. The appearance of the lesions and the scarring were consistent with a late syphilid, but Dr. Smith thought they were probably tuberculous in character.

DISCUSSION

DR. CORLETT said that clinically the lesion over the scapula was distinctly tuberculous in appearance and that some of the later lesions elsewhere were typical of lupus. Some of the shiny patches which had appeared more recently had a striking resemblance to lichen planus. Dr. Smith had suggested that those lesions had undergone involution and that the lesions which appeared to be quite flat would subsequently assume the appearance of the typical lesions of lupus, which he thought explained the apparent incongruity, and, therefore, he would regard the case as one of tuberculosis cutis.

DR. PUSEY agreed with the diagnosis. He thought it was a case of lupus erythematoides.

DR. ORMSBY said the lesions on the thigh were typical tubercular nodules like the others. Erythematoid lupus vulgaris presents a very different picture, and he did not consider this case an example of this type.

DR. PUSEY said lupus erythematoides was not a combination of these two but a lupus vulgaris with the appearance of lupus erythematosus — erythematosus-like lesions, but not a combination or mixed type.

DR. HIGHMAN thought the lesions resolved themselves easily into lupus nodules.

DR. POLLITZER said the first case of lupus vulgaris erythematoides was published by Leloir in 1890 and represented a disease which at first glance was lupus erythematoide, more or less extensive plaques with scaling, which, on close inspection, presents something of the appearance of lupus vulgaris. A diagnosis was possible from the histologic structure and experimental inoculations rather than the clinical picture.

DR. GOLDENBERG thought the colored girl with the three phases of tuberculosis had a typical case of Leloir's lupus vulgaris erythematoides.

HODGKIN'S DISEASE. Presented by Dr. White.

A man, aged 30 years, presented multiple pea-sized and larger nodules distributed over the body and extremities. There were literally hundreds of these round and almond shaped tumors which were firm but not hard and produced no change in the color or the texture of the overlying skin.

The patient had been sent up from the medical ward for diagnosis of his cutaneous symptoms. There was a history of "stomach trouble" of eight years' duration and of a strongly positive Wassermann reaction.

Blood examination made in the hospital revealed 2,784,000 red cells and 2,400 white cells; the color index was 0.98; hemoglobin content was 53 per cent. (Sahli). The differential count was: 94 per cent. large lymphocytes, 4 per cent. small lymphocytes and 2 per cent. polymorphonuclears.

DISCUSSION

Dr. Schamberg believed it to be a case of leukemia of the skin.

SARCOMA. Presented by Dr. White.

A man, aged 60 years, who presented lesions on the left leg, had a history of a street-car accident in November, 1920. In February, 1921, two nodules began to appear on the left leg and had persisted since that time. These were quite alike and consisted of decidedly hard, protuberant masses the size of mandarin oranges and the color of raw beef.

DISCUSSION

Dr. Haase said regardless of the fact that some of the lesions had disappeared he believed they were sarcomas.

PSORIASIS. Presented by Dr. Oliver.

A man, aged 33 years, presented lesions of psoriasis that were limited to the abdomen and back, covering large areas in these situations.

PRIMARY LESION OF THE TONGUE. Presented by Dr. Smith.

A man, aged 54 years, who worked in a large industrial plant where a common drinking cup was used, had been admitted to the surgical ward for a supposed epithelioma of the tongue. There he was seen in consultation and a diagnosis of a primary lesion of the tongue was made. He received two injections of arsphenamin within three or four days; then he was put on weekly treatments, and the condition cleared up and remained well for some time. He then returned with a strongly positive Wassermann reaction and received another course of treatment. Following that he developed a generalized exfoliative dermatitis which, in the course of six weeks, subsided, and his general condition became good in two months. Following that there gradually developed a parakeratotic condition, definitely marginated and quite pruritic, and the clinical picture was that of parakeratosis verging into mycosis fungoides, but sections from the infiltrated areas showed only the marked parakeratosis. Dr. Towle said that the tumors were identical with those of the woman he had exhibited.

DISCUSSION

Dr. Wile thought it was lichen planus. He thought the lesions on the buccal mucosa and on the glans penis were typical of lichen planus. The hyperpigmentation might have been due to the arsenic.

DR. GOLDENBERG agreed with Dr. Wile's diagnosis.

DR. FORDYCE thought it was well for the members of the Association to read up on the arsenic epidemic which occurred in England twenty years ago from poisoning of the beer supply. The description of the skin lesions during that epidemic would correspond to the lesions in this case. There was thickening of the skin, and bullous and pustular lesions without the chronic effect of arsenic on the skin.

DR. SUTTON said that in the beer cases there were no lesions on the mucosa of the mouth.

DR. ORMSBY called attention to the fact that the lesions in the mouth extended along the margin at the junction of the teeth. These lesions were not individual, but were plaques identical with those commonly seen in leukoplakia. He had seen the cases of arsenical dermatitis in London, and a number of the lesions on this patient's skin simulated those very closely. He could not see any lesions that could be definitely said to be those of lichen planus. A biopsy had been made which did not show the structure of lichen planus, and the latter is a disease that can be diagnosed microscopically.

DR. HIGHMAN thought it was curious how people looking at the same thing formed such different ideas of what they saw. He did not pay much attention to the skin of this patient after looking in the mouth and seeing the typical lesions of lichen planus. He thought the lesions on the skin were involuted lesions of lichen planus. The color of the lesions on the lower part of the trunk seemed quite characteristic of faded lichen planus, and the typical lesion on the glans penis seemed to him to satisfy all the phases of the question that needed to be satisfied.

HYPOTHYROIDISM. Presented by DR. TOWLE.

Te patient was a child, aged 4 years, whose case is reported in detail in a paper entitled "Hypothyroidism with Unusual Skin Manifestations," to be published in the ARCHIVES.

LUPUS VULGARIS WITH ELEPHANTIASIS OF THE FACE. Presented by DR. TOWLE.

A boy, aged 17 years, who lived in a rural New England village, four years ago suffered a mild frostbite of both cheeks. Three years ago, during the cold weather, both cheeks swelled and an eruption developed. With the onset of warm weather the swelling disappeared. The symptoms recurred with cold weather and disappeared with warm weather. Last winter the swelling recurred as before, but this spring it failed to disappear.

On entrance to the hospital the boy presented an upper lip which was so swollen as to impinge on the nostrils. From the ala on either side an outwardly curved band of ulceration ran downward to the corners of the mouth. Within, the surface was bluish-red and studded with pinhead to pea-sized greenish-yellow crusts. At either corner of the mouth was a lesion, 1 inch in diameter, which clinically suggested epitheliomas. On palpation the swollen lip gave a sense of deep fluid infiltration. Nowhere were there visible any typical lupus nodules, but under the microscope typical tubercles were present.

Hot and cold boric acid wet packs had caused the swelling of the lip to lessen greatly, and after the use of the quartz lamp, pyrogallic preparations and various other caustics the tuberculous lesions had improved.

DISCUSSION

Dr. Sutton thought the condition looked like lupus vulgaris.

GENERALIZED DERMATOSIS. Presented by Dr. Burns.

The patient was a man, whose disorder began fifteen years ago, appearing first on the face. Gradually, with varying remissions, it spread to the trunk, the upper limbs, and to a small extent to the lower limbs. The process was characterized by infiltrated, papular lesions, followed almost invariably by a certain amount of atrophy. When the patient was first seen in consultation, Dr. Burns was inclined to call the condition a case of dermatitis chronica atrophica, although it was not typical of this disorder. He had had no opportunity to examine the patient carefully since that time, as he had just returned to the hospital.

DISCUSSION

Dr. Lane said it had been suggested that this might be a case of poikiloderma atrophicans vasculare. He thought that possible and that a further study would be necessary for decision of the question, because the cases so far reported were too few to have definitely fixed the limits of the variation of appearances in that disease. This case, however, showed some marked differences from his case and those previously described. The most striking difference was that in this case the most marked changes were at the edges rather than at the center of the lesions. In other cases there was marked lividity at the center of the older lesions. This was absent here, and there was also little atrophy. The pigmentation of this case was less distinct than in previously reported cases. He hoped that Drs. Wise and Ormsby would give their impression of the case.

Dr. Ravogli said the case impressed him with the possibility of Majocchi's disease on account of the discoloration and the small nodules disposed in circles in the hand. He thought it was probably an aggravated case, which had after a long time caused atrophy of the skin.

Dr. Ormsby considered the case entirely different from anything he had ever seen. While in some respects it resembled the case they had had under observation, in other respects it was very different. In their case the lesions resembled a healed radio-dermatitis, but in this case no lesions of this type were present. He could not be sure that there was telangiectasia and, taken as a whole, the case was very different.

Dr. Wise thought the interpretation of the case was almost impossible without further study. In regard to Dr. Ravogli's statement that it might be Majocchi's disease, that could be eliminated. Those cases had not widespread atrophy, and in this patient it would be courageous to say that it was more likely that disease than any other clinical conception of anything in the literature. He believed further study would prove it to be that disease. Five years from now the skin may take on the typical appearance of Dr. Lane's case, and resemble an old cured radiodermatitis, which poikiloderma resembles.

Dr. Foerster said that in the *Ikonographia* a case is described by Jamieson without diagnosis in which the clinical picture bears resemblance to this condition in several respects.

Dr. Pusey asked whether there was anything in Dr. Lane's case of poikiloderma analogous to the infiltrated appearance which precedes the atrophy in these cases.

DR. LANE said there was never any elevation of the skin in his case. The new lesions, where the process was spreading, were first pigmented around the hair follicles; then the inflammatory process appeared and later the atrophy.

DR. PUSEY thought this patient would not have telangiectasia later for he did not have that kind of skin. The infiltrative process at the border was probably the primary process. He could see no evidence of secondary telangiectasia.

DR. MCEWEN said the patient told him the process had been going on for fifteen years.

DR. LANE said that in his case every one had remarked on the resemblance to angioma serpiginosum. There was no such likeness in this case.

DR. BURNS said the patient was seen first in the surgical ward in consultation. Only a short examination had been made at that time and he asked to have the man transferred to the dermatologic ward when discharged. The tissue instead of being sent to him was sent to the general laboratory and was lost. They hoped to be able to elucidate some of the points brought up by the discussion. In presenting the case he felt embarrassed because he had had no opportunity to study the patient and had no adequate history, so presented the case for diagnosis. The disorder had been present for fifteen years.

DR. HAASE said that without ever having seen a similar case, he would hazard a diagnosis of a diffuse tuberculosis of the skin of some form, advancing, leaving scar tissue behind.

DR. WALLHAUSER agreed with Dr. Haase. The peculiar lupoid nodular border was strongly suggestive of a tuberculous process.

Index to Current Literature

DERMATOLOGY

Actinomycosis, Peculiar Case of. J. Riising, Ugesk. f. Læger **83**:833 (June 23) 1921.

Addison's Disease, Pigmentation in. A. Bittorf, Deutsch. Arch. f. klin. Med. **136**:314 (July 5) 1921.

Anthrax, Human, in Buganda Kingdom, Case of. W. L. Peacock and H. L. Duke, Lancet **2**:332 (Aug. 13) 1921.

Anthrax Infection, Native Preventives of. J. Lewis and O. F. Gibbs, South African M. Rec. **19**:232 (June 25) 1921.

Anthrax, Occurrence of, in Navy; Its Diagnosis and Prevention. P. W. Bassett-Smith, J. State Med. **29**:249 (Aug.) 1921.

Anthrax, Symptomatic, Bacteriologic Studies on. Uchimura, Deutsch. med. Wchnschr. **47**:738 (June 30) 1921.

Chaulmoogra Oil in Leprosy and Tuberculosis. L. Rogers, Lancet **1**:1178 (June 4) 1921.

Chickenpox and Smallpox, Differentiation of. E. Romanelli, Policlinico **28**: 978 (July 18) 1921.

Chickenpox, Relation of Herpes Zoster to. W. M. Kraus, New York M. J. **114**:162 (Aug. 3) 1921.

Cylindroma of the Tongue. O. Preusse, Beitr. z. klin. Chir. **122**:355, 1921.

Dermatology, Uses of Ultra-Violet Rays in. R. B. Josselyn, J. Maine M. A. **11**:383 (July) 1921.

Eczemas, Chronic, Etiology and Therapy of. Hilgermann, München. med. Wchnschr. **68**:702 (June 10) 1921.

Eczema, General and Dietetic Treatment of. J. P. C. Griffith, New York M. J. **114**:153 (Aug. 3) 1921.

Eczema in Breast-Fed Baby and Protein Sensitization. E. S. O'Keefe, Boston M. & S. J. **185**:194 (Aug. 18) 1921.

Epidemic Encephalitis, Herpes in. A. Netter, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1135 (July 15) 1921.

Erythema Nodosum, Nature and Import of. H. Ernberg, Jahrb. f. Kinderh. **95**:1, 1921.

Goiter, Exophthalmic, Skin Rashes in. F. F. Gundrum, California State J. M. **19**:339 (Aug.) 1921.

Herpes in Epidemic Encephalitis. A. Netter, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1135 (July 15) 1921.

Herpes Zoster Ophthalmicus, Case of. S. K. Ganguly, Indian M. Gaz. **56**:211 (June) 1921.

Herpes Zoster, Relation of, to Chickenpox. W. M. Kraus, New York M. J. **114**:162 (Aug. 3) 1921.

Leprosy and Tuberculosis, Chaulmoogra Oil in. L. Rogers, Lancet **1**:1178 (June 4) 1921.

Leprosy, Epidemiologic Study of Endemic Focus of. M. F. Boyd and W. F. Fox, Am. J. Pub. Health **11**:628 (July) 1921.

Leprosy in Northern Brazil. A. Da Matta, Brazil-med. **35**:287 (June 4) 1921.

Leprosy, Suspected, Case of. J. W. W. Stephens and S. Adler, Ann. Trop. M. & Parasitol. **15**:173 (July) 1921.

Leukemia, Lymphatic, Pemphigoid Skin Eruption in. Sachs, Wien. klin. Wchnschr. **34**:317 (June 30) 1921.

Lupus, Carbon Dioxid Snow in. J. González Urueña, Gac. méd. de Mexico **1**:424 (Aug.-Dec.) 1921.

Lupus, Treatment of, in General Practice. Engwer, Therap. Halbmonatsh. **35**:257 (May 1) 1921.

Measles at Montevideo. V. Zerbino, Rev. med. d. Uruguay **24**:258 (June) 1921.

Measles, Contagiousness of. M. Bauer, München. med. Wchnschr. **68**:736 (June 17) 1921.

Measles, Prolongation of Incubation in, by Infections. Bauer, München. med. Wchnschr. **68**:736 (June 17) 1921.

Melanodermia, Phthiriasis with. L. Tixier and H. Duval, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1046 (July 8) 1921.

Melanodermia, Unilateral. R. A. Gutmann and J. Dalsace, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1062 (July 8) 1921.

Mongolian Blue Spot in Two Children. J. Comby, Arch. de méd. d. enf. **24**: 366 (June) 1921.

Mouth, Carcinoma of, Roentgenotherapy in. W. Baensch, München. med. Wchnschr. **68**:810 (June 30) 1921.

Nipple, Paget's Disease of. S. Sekiguchi, Mitt. a d. Path. Inst. Univ., Sendai Japan **1**:385 and 393 (May 11) 1921.

Oriental Sore in Russian Turkestan and Results of Treatment with Injections of Tartar Emetic Solution. J. A. Sinton, Ann. Trop. M. & Parasitol. **15**:107 (July) 1921.

Paget's Disease of the Nipple. S. Sekiguchi, Mitt. a. d. Path. Inst. Univ., Sendai, Japan **1**:385 and 393 (May 11) 1921.

Phthiriasis with Melanodermia. L. Tixier and H. Duval, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1046 (July 8) 1921.

Psoriasis. P. G. Unna, Wien. klin. Wchnschr. **34**:275 (June 9) 1921.

Psoriasis, Case of. A. Viswalingam, J. Trop. M. **24**:192 (July 15) 1921.

Seborrheic Rosacia. P. G. Unna, München. med. Wchnschr. **68**:701 (June 10) 1921.

Skin Diseases, Etiology of. A. Whitfield, Lancet **2**:168 (July 23) 1921.

Skin Diseases. Pathology of Ringworm and Allied Skin Diseases. A. N. Srivastava, Indian M. Gaz. **56**:213 (June) 1921.

Skin Diseases, Psychogenic and Neurogenic Factors in. M. Scholtz, Med. Rec. **100**:234 (Aug. 6) 1921.

Skin Eruption, Pemphigoid, in Lymphatic Leukemia. Sachs, Wien. klin. Wchnschr. **34**:317 (June 30) 1921.

Skin in Relation to Constitution. H. v. Hoesslin, München. med. Wchnschr. **68**:797 (June 30) 1921.

Skin Rashes in Exophthalmic Goiter. F. F. Gundrum, California State J. M. **19**:339 (Aug.) 1921.

Smallpox and Chickenpox, Differentiation of. E. Romanelli, Policlinico **28**: 978 (July 18) 1921.

Smallpox, Injection of Lymph Subcutaneously as a Protection Against. C. F. Fearnside, Indian J. M. Res. (Special Indian Science Congress Number), 1920, p. 71.

Smallpox, Protection Against. G. B. Gruber, München. med. Wchnschr. **68**: 778 (June 24) 1921.

Sporotrichosis; Case Report. C. E. Tennant and W. S. Dennis, Colorado Med. **18**:165 (Aug.) 1921.

Tongue, Cylindroma of. O. Preusse, Beitr. z. klin. Chir. **122**:355, 1921.

Tuberculosis and Leprosy, Chaulmoogra Oil in. L. Rogers, Lancet **1**:1178 (June 4) 1921.

Ultra-Violet Rays, Uses of, in Dermatology. R. B. Josselyn, J. Maine M. A. **11**:383 (July) 1921.

SYPHILOLOGY

Alopecia and Syphilis, Relations Between. R. Sabouraud, Presse méd. **29**:581 (July 23) 1921

Anemias of Syphilis. J. Eason, Brit. M. J. **2**:186 (Aug. 6) 1921.

Aortitis, Syphilitic. A. G. Gibson, Brit. M. J. **2**:188 (Aug. 6) 1921.

Arsphenamin, Jaundice After. P. Tachau, Deutsch. med. Wchnschr. **47**:711 (June 23) 1921.

Arsphenamin, Use of: Its Effect on Kidneys and Its Therapeutic Results. H. B. Anderson, Am. J. M. Sc. **162**:80 (July) 1921.

Bronchi and Trachea, Syphilis of; Résumé of Diagnostic Features; Three Case Reports. P. M. Stimson, Am. J. M. Sc. **161**:740 (May) 1921.

Central Nervous System, Syphilis of. J. Hagelstam, Finska Läk.-Sällsk. Handl. **63**:223 (May-June) 1921.

Chancre, Mixed, Diagnosis of. G. Thibierge and P. Legrain, Presse méd. **29**:563 (July 16) 1921.

Chancroidal Infections. W. F. Pearce, U. S. Nav. M. Bull. **15**:554 (July) 1921.

Circumcision Prevents Syphilis. A. Irvine, Virginia M. Month. **48**:214 (July) 1921.

Condylomas in Children with Hereditary Syphilis, Secondary Infection with Diphtheria Bacilli in. W. Hedrich, München. med. Wchnschr. **68**:813 (June 30) 1921.

Corpuscles, Red, in Infancy, Speed of Sedimentation of; Especially in Congenital Syphilis. P. György, München. med. Wchnschr. **68**:808 (June 30) 1921.

Endocrine Glands and Functional Syphilis. P. Merklen, Médecine **2**:774 (July) 1921.

Heart, Syphilis of. J. Cowan and J. K. Rennie, Brit. M. J. **2**:184 (Aug. 6) 1921.

Jaundice After Arsphenamin. P. Tachau, Deutsch. med. Wchnschr. **47**:711 (June 23) 1921.

Jaundice, Case of, from Late Salvarsan Poisoning. J. Elliott, Lancet **1**:1180 (June 4) 1921.

Kidneys, Syphilitic Disease of. W. A. Weisfelt, Nederlandsch Tijdschr. v. Geneesk. **1**:3073 (June 4) 1921

Liver, Syphilitic Cirrhosis of. F. Saint-Girons, Médecine **2**:779 (July) 1921.

Liver, Tertiary Syphilis of. T. W. Tallqvist, Finska Läk.-Sällsk. Handl. **63**:261 (May-June) 1921.

Neosalvarsan, Administration of. J. B. Bostick, U. S. Nav. M. Bull. **15**:536 (July) 1921.

Neurosyphilis. M. Staemmler, Deutsch. Arch. f. klin. Med. **136**:271 (July 5) 1921.

Neurosyphilis, Diagnosis of. B. Rodriguez Arias, Rev. Española de med. y cirug. **4**:202 (April) 1921.

Neurosyphilis, Treatment of. A. Keidel, South. M. J. **14**:595 (Aug.) 1921.

Osteomyelitis and Syphilis. F. Rodríguez Gómez, Rev. med. d. Uruguay **24**: 254 (June) 1921.

Paresis, Spirochetes in Visual Tract in. Igersheimer, Deutsch. med. Wchnschr. **47**:738 (June 30) 1921.

Phlebitis, Primary Syphilitic. Y. Manouélian, Gynéc. et Obst. **3**:407, 1921.

Salvarsan Poisoning, Late, Case of Jaundice from. J. Elliott, Lancet **1**:1180 (June 4) 1921.

Spirocheta Pallidum, Preservation of Stock Strains of, and One Demonstration of Infection in Rabbits. W. H. Brown and L. Pearce, J. Exper. M. **34**: 185 (Aug.) 1921.

Spirochetes in Visual Tract in Paresis. Igersheimer, Deutsch. med. Wchnschr. **47**:738 (June 30) 1921.

Stomach, Syphilis of. F. C. Rinker, Virginia M. Month. **48**:278 (Aug.) 1921.

Stomach, Syphilitic Disease of. R. Sparman, Deutsch. Ztschr. f. Chir. **164**:136 (June) 1921.

Syphilis, Active, Latent-Active and Inactive. T. E. H. Thaysen, Ugesk. f. Læger **83**:759 (June 9) 1921.

Syphilis and Alopecia, Relations Between. R. Sabouraud, Presse méd. **29**:581 (July 23) 1921.

Syphilis and Osteomyelitis. F. Rodríguez Gómez, Rev. med. d. Uruguay **24**: 254 (June) 1921.

Syphilis, Anemias of. J. Eason, Brit. M. J. **2**:186 (Aug. 6) 1921.

Syphilis, Case of, Innocently Acquired with Primary Lesion on Palm of Left Hand. J. W. Jones, U. S. Nav. M. Bull. **15**:556 (July) 1921.

Syphilis, Cerebromeningeal. A. Florand and P. Nicaud, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1110 (July 15) 1921.

Syphilis, Circumcision Prevents. A. Irvine, Virginia M. Month. **48**:214 (July) 1921.

Syphilis, Experimental, in Rabbit. Affections of Eyes. W. H. Brown and L. Pearce, J. Exper. M. **34**:167 (Aug.) 1921.

Syphilis, Functional, and Endocrine Glands. P. Merklen, Médecine **2**:774 (July) 1921.

Syphilis, Infantile, Treatment of. S. Engel and M. Türk, Therap. Halbmonatsh. **35**:242 (April 15) 1921.

Syphilis. Iodin-Phosphoric Acid Reaction in Urine in Syphilis. R. A. Kilduffe, Med. Rec. **100**:329 (Aug. 20) 1921.

Syphilis, Management of, at Bellevue Hospital. M. B. Parounagian, J. M. Soc. New Jersey **18**:242 (Aug.) 1921.

Syphilis of Heart. J. Cowan and J. K. Rennie, Brit. M. J. **2**:184 (Aug. 6) 1921.

Syphilis of Stomach. F. C. Rinker, Virginia M. Month. **48**:278 (Aug.) 1921.

Syphilis of the Central Nervous System. J. Hagelstam, Finska Läk.-Sällsk. Handl. **63**:223 (May-June) 1921.

Syphilis of Trachea and Bronchi; Résumé of Diagnostic Features; Three Case Reports. P. M. Stimson, Am. J. M. Sc. **161**:740 (May) 1921.

Syphilis. Primary Syphilitic Phlebitis. Y. Manouélian, Gynec. et Obst. **3**: 407, 1921.

Syphilis, Protection of Public Against. A. Vernes, Internat. J. Pub. Health **2**:147 (March-April) 1921.

Syphilis, Reliability of Herman and Perutz' Precipitating Reaction of. M. Hirano, Bull. Naval M. A., Tokyo, March, 1921, p. 2.

Syphilis a Rural Problem. W. J. Highman, J. A. M. A. **77**:583 (Aug. 20) 1921.

Syphilis. Secondary Infection with Diphtheria Bacilli in Condylomas in Children with Hereditary Syphilis. W. Hedrich, München. med. Wchnschr. **68**:813 (June 30) 1921.

Syphilis. Speed of Sedimentation of Red Corpuscles in Infancy; Especially in Congenital Syphilis. P. Gyorgy, München. med. Wchnschr. **68**:808 (June 30) 1921.

Syphilis, Tertiary, of the Liver. T. W. Tallqvist, Finska Läk.-Sällsk. Handl. **63**:261 (May-June) 1921.

Syphilis, Treating. L. L. Michel and H. Goodman, New York M. J. **114**:102 (July 20) 1921.

Syphilis, Value of Therapeutic Methods in. Spiethoff, München. med. Wchnschr. **68**:801 (June 30) 1921.

Syphilis, Visceral. H. C. Jacobaeus, Finska Läk.-Sällsk. Handl. **63**:241 (May-June) 1921.

Syphilis, Visceral. T. C. Allbutt, Brit. M. J. **2**:177 (Aug. 6) 1921.

Syphilitic Aortitis. A. G. Gibson, Brit. M. J. **2**:188 (Aug. 6) 1921.

Syphilitic Cirrhosis of Liver. F. Saint-Girons, Médecine **2**:779 (July) 1921.

Syphilitic Disease of Kidneys. W. A. Weisfelt, Nederlandsch Tijdschr. v. Geneesk. **1**:3073 (June 4) 1921.

Syphilitic Disease of the Stomach. R. Sparman, Deutsch. Ztschr. f. Chir. **164**:136 (June) 1921.

Syphilitic Fever. G. Gautier, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:1134 (July 15) 1921.

Syphilitic Out-Patient, Male, Inadequate Attendance of. R. E. Roberts, Lancet **2**:277 (Aug. 6) 1921.

Syphilitics, Polariscopic Study of Urines of Group of. S. P. Taylor and K. P. A. Taylor, Am. J. M. Sc. **162**:47 (July) 1921.

Trachea and Bronchi, Syphilis of; Résumé of Diagnostic Features; Three Case Reports. P. M. Stimson, Am. J. M. Sc. **161**:740 (May) 1921.

Venereal Diseases. Antivenereal Prophylaxis. F. Neufeld, Deutsch. med. Wchnschr. **47**:737 (June 30) 1921.

Venereal Infection, Prevention of. T. E. Satterthwaite, Med. Rec. **100**:311 (Aug. 20) 1921.

Venereal Prophylaxis. J. S. Gomez, Military Surgeon **49**:33 (July) 1921.

Viscera, Syphilis of. T. C. Allbutt, Brit. M. J. **2**:177 (Aug. 6) 1921.

Visual Tract in Paresis, Spirochetes in. Igersheimer, Deutsch. med. Wchnschr. **47**:738 (June 30) 1921.

Wassermann Reaction, Notes on. W. J. Tulloch, Edinburgh M. J. **27**:34 (July) 1921.

Wassermann Reaction, Spontaneous Variations in Strength of. T. E. Hess Thaysen, Acta Med. Scandinavica **55**:281 (June 17) 1921.

Wassermann Reaction, Standardization of. J. A. Kolmer, J. A. M. A. **77**:776 (Sept. 3) 1921.

Wassermann Test and Its Interpretation. R. L. Kahn, J. Lab. & Clin. M. **6**:579 (July) 1921.